Improved detection of hepatic metastases at the time of curative resection of colorectal cancer by iodised oil emulsion enhanced computerised tomography and intraoperative ultrasonography.

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W.F. Anthony Miles,

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Abstract

Up to 30% of patients who undergo colonic resection for colorectal cancer have spread of their disease, to the liver, at the time of operation. In 50% of these patients the metastases are so small that they cannot be detected either by preoperative ultrasonography or by visualisation and palpation of the liver at the time of surgery. Patients who have hepatic metastases have a poor prognosis.

Hepatic resection for colorectal metastases offers a survival advantage of 25% at five years. At present about half of the patients with hepatic metastases are picked-up during follow-up by which time only a small percentage have resectable disease.

This thesis proposes that IOUSS and IOE scanning may be effective in the detection of small metastases at the time of primary colon resection, and that IOE scanning in the follow up period will detect new metastases as they develop. Patients who have metastases detected in this way will be suitable for hepatic resection and have an improved 5 year survival. The detailed staging of patients with regard to hepatic metastases has been used to clarify the relationship between the presence of hepatic metastases, and elevation in the level of serum CEA.

Iodised oil enhanced CT (IOE) scanning, intra-operative ultrasonography (IOUSS) and dynamic bolus enhanced CT scanning are used to detect hepatic malignancy prior to hepatic resection. The accuracy of each technique is calculated. IOE scanning is shown to be the most accurate preoperative investigation to determine resectability in patients with hepatic malignancy. The serum level of carcinoembryonic antigen is also related to the presence of hepatic metastases from colorectal cancers at the time of hepatic resection.

IOUSS is shown to be as accurate as IOE scanning in the detection of patients with metastases at the time of operation and detects more patients with metastases than IOE scanning, although this difference does not reach statistical significance.

IOE scanning can detect the appearance and growth of metastases in patients following colonic resection, however, it cannot be used as a routine form of follow-up as patients are reluctant to undergo repeated scans over a two year period.

IOE scanning and IOUSS are able to detect very small hepatic metastases in patients following colonic surgery. Two patients with small metastases went on to have a hepatic resection. Unfortunately both of these patients died within 2 years of hepatic surgery. Early detection of metastases by IOE and IOUSS scanning did not therefore improve patients' survival. The results of IOE scanning and IOUSS have been used to define levels of serum CEA which are likely to be related to the presence of hepatic metastases both at the time of colonic resection and during follow up.

In conclusion IOUSS is shown to be a sensitive and accurate method of detecting hepatic metastases from colorectal cancer and should be undertaken at the time of resection of primary colorectal cancers. The information gained improves staging and estimation of prognosis.

Confirmation of originality.

I confirm that the work contained within this Thesis is original and my own, except where the work of others is appropriately acknowledged.

W.F. Anthony Miles, 1995

Abbreviations

BP	British Pharmacopoeia
CEA	Carcinoembryonic antigen
cm	Centimetres
CRT	Cathode Ray Tube
CT	Computerised axial tomography
dB	Decibels
DBCT	Dynamic bolus enhanced CT scanning
EGH	Eastern General Hospital
IOE	Iodised Oil Emulsion enhanced CT scanning
IOUSS	Intraoperative ultrasound scanning
l	Litres
MHz	Megahertz
mbq	Millibecquerels
mg	Milligrams
mm	Millimetres
RIE	The Royal Infirmary of Edinburgh
TGC	Time gain compensation
USS	Ultrasound scan
WGH	Western General Hospital

Dedication

To my wife Liz and children, Sophie and Kristian.

Publications and Presentations of work contained in this thesis.

Papers

Miles W.F.A. Paterson-Brown S. Garden O.J. Laparoscopic contact hepatic ultrasonography. *British Journal of Surgery* 1992; **79**: 419-420.

Mahadaven M. Paterson-Brown S. Windsor J. Miles W.F.A. Garden O.J. Early experience of laparoscopic ultrasonography in the management of pancreatic carcinoma. *Surgical Endoscopy* 1993; **7**: 177-181.

Miles W.F.A. Greig J.D. Seth J. Sturgeon C. Nixon S.J. Carcinoembryonic antigen and a follow-up algorithm for patients with colorectal cancer.*British Jounal of General Practice* In Press

Miles WFA, Greig JD, Seth J, Sturgeon C, Nixon SJ. Carcinoembryonic antigen in the follow-up of patients with colorectal cancer. *Lothian surgical Audit Report* 1994 .

John T.G. Greig J.D. Crosbie J. Miles W.F.A. Garden O.J. Superior staging of liver tumours with laparoscopy and laparoscopic ultrasound *Annals of Surgery* 1994; **220**: 711-719.

Published Abstracts

Miles W.F.A. Crosbie J. Turnbull L. Allan P. Garden O.J. Intraoperative ultrasonography and enhanced computed tomography in the detection of hepatic metastases. *British Journal of Surgery* 1993; **80**: S51

Presentations

Royal College of Surgeons of Edinburgh
October 1993
Saturday morning meeting
CEA in the follow up of colorectal cancer

3rd European congress of Surgery London
September 1993
Intraoperative ultrasonography and enhanced C.T. scanning in the detection of hepatic metastases.

Combined meeting of the Association of Surgeons of Great Britain and Northern Ireland and Trinity 400
Dublin Ireland 22nd September 1992
Assessing the resectability of hepatic tumours by enhanced C.T. scanning.

Royal College of Surgeons Edinburgh 1992
Saturday morning meeting
Iodised Oil Emulsion and Intraoperative ultrasonography in the detection of hepatic metastases from colorectal cancer
October 1992

Royal College of Surgeons Edinburgh 1991
School of Surgery day
Iodised Oil Emulsion enhanced C.T. scanning compared to conventional techniques in preoperative assessment of
hepatic malignancy

World Congress of Surgery Stockholm 1991
Iodised oil emulsion and intra-operative ultrasound in the detection of colo-
rectal hepatic metastases

Dumfries and Galloway Hospital 1991
Detection of Hepatic tumours

Posters

3rd European congress of Surgery London 1993
Intraoperative ultrasonography and enhanced C.T. scanning in the detection of hepatic metastases

Videos

Intraoperative Ultrasonography of the liver and hepatic malignancy

Chapter I

History of staging and surgery for colorectal cancer

I.A. Introduction

I.A.1. Hepatic metastases

Colonic cancer often spreads to the liver as the first site of extra lymphatic disease (Hogg IL, 1956) and may represent the only site of spread in up to 32% of patients following apparently curative resection of their primary cancer (Russell AH, 1984). The presence of hepatic metastases is the single most powerful prognostic indicator following apparently curative colonic resection. Up to 90% of patients with hepatic metastases succumb in the 24 months following surgery (Bengmark S, 1969; Wagner JS, 1984; Arnaud JP, 1984). Current surgical practice relies on pre-operative ultrasonography and palpation at the time of operation to detect hepatic metastases. Both of these methods have been shown to be insensitive and inaccurate (Gunven P, 1985; Finlay IG,1986).

Intraoperative ultrasonography (IOUSS) is a sensitive and accurate method of detecting intrahepatic tumours (Sheu J-C, 1985; Rifkin MD, 1987; Parker GA, 1989; Clarke MP, 1989; Olsen AK, 1990; Charnley RM, 1991; Machi J, 1991). It is possible that this technique may be used to improve the detection of hepatic metastases at the time of operation, reducing the number of metastases that remain occult. Early detection of otherwise occult metastases may improve staging, better define prognosis and increase the detection of patients with resectible hepatic metastases. Early resection may in turn lead to an improvement in survival. The overall survival of patients with colorectal cancer has not changed in the last 50 years (Scottish Cancer Registry 1990).

I.A.1.a. Why the liver?

Malignant tumours shed cells into their venous drainage. Colorectal cancers drain via the portal venous system which, except in very special circumstances, drains solely to the liver. Turnbull has shown that during tumour manipulation portal blood contains viable tumour cells singly and in clumps (Turnbull RB (Jr), 1967) which pass into the hepatic capillary bed (Wiggers T, 1988;1990). Not all of these tumour cells successfully implant. Weiss has proposed a theory of metastatic inefficiency (Weiss L, 1990) in that the rate of tumour cell

delivery to the liver is at least 1,000 times greater than the number of metastases that appear. At a late stage in their development, liver metastases shed viable tumour cells into the hepatic veins and via the vena cava into the pulmonary capillary bed. Only 1:1,000 or less of the malignant cells delivered to the lungs successfully implant (Sugarbaker PH, 1990).

The portal route of spread applies to nearly all colorectal cancers; only in very low rectal cancers is there any direct access to the systemic venous circulation by tumour cells. The majority of tumour cells delivered to the liver do not survive; however the mechanism of their destruction is not understood. Only a very few cells successfully implant (*Plate 1.*) and form a detectable metastases (*Plate 2.*).

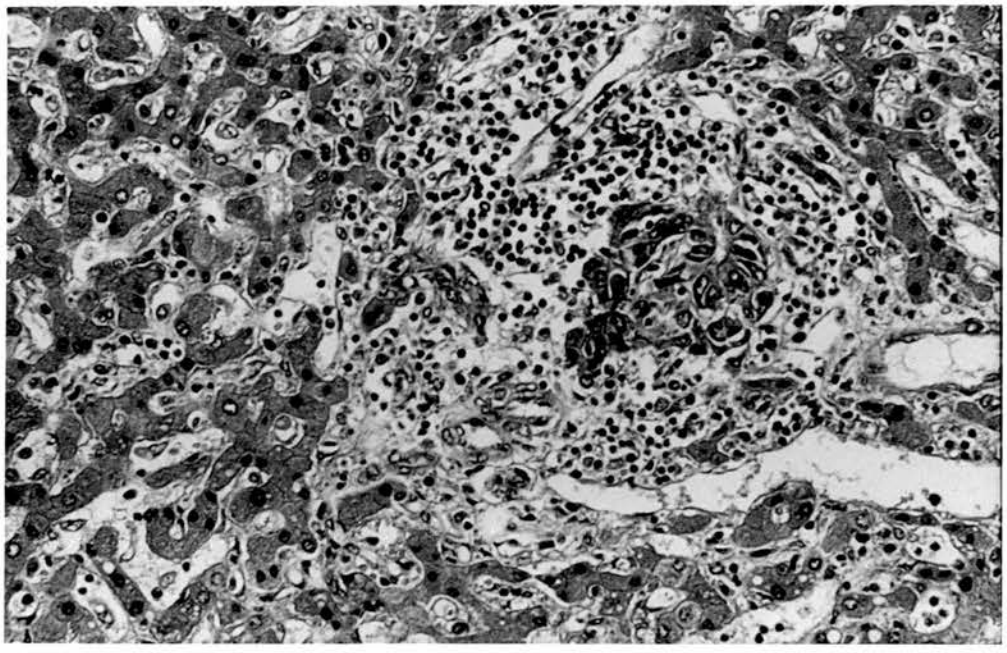

Plate 1. A micro metastasis from a colon cancer: found in the resected specimen from a patient with an apparently solitary metastasis in the right hemi liver.

Implantation and growth are not a random events, the population of cells shed into the circulation exhibit various levels of ability to form metastases. It has

been shown that cloned sub populations of cells from a metastasis will form a larger number of new metastases (when reintroduced to immunologically nude mice) than cells cloned at random from the parent tumour (Poste G, 1980). Individual cell lines cloned from the parent tumour will also show variation in their ability metastasise. Once a single cell line has been cloned then its level of successful implantation remains constant.

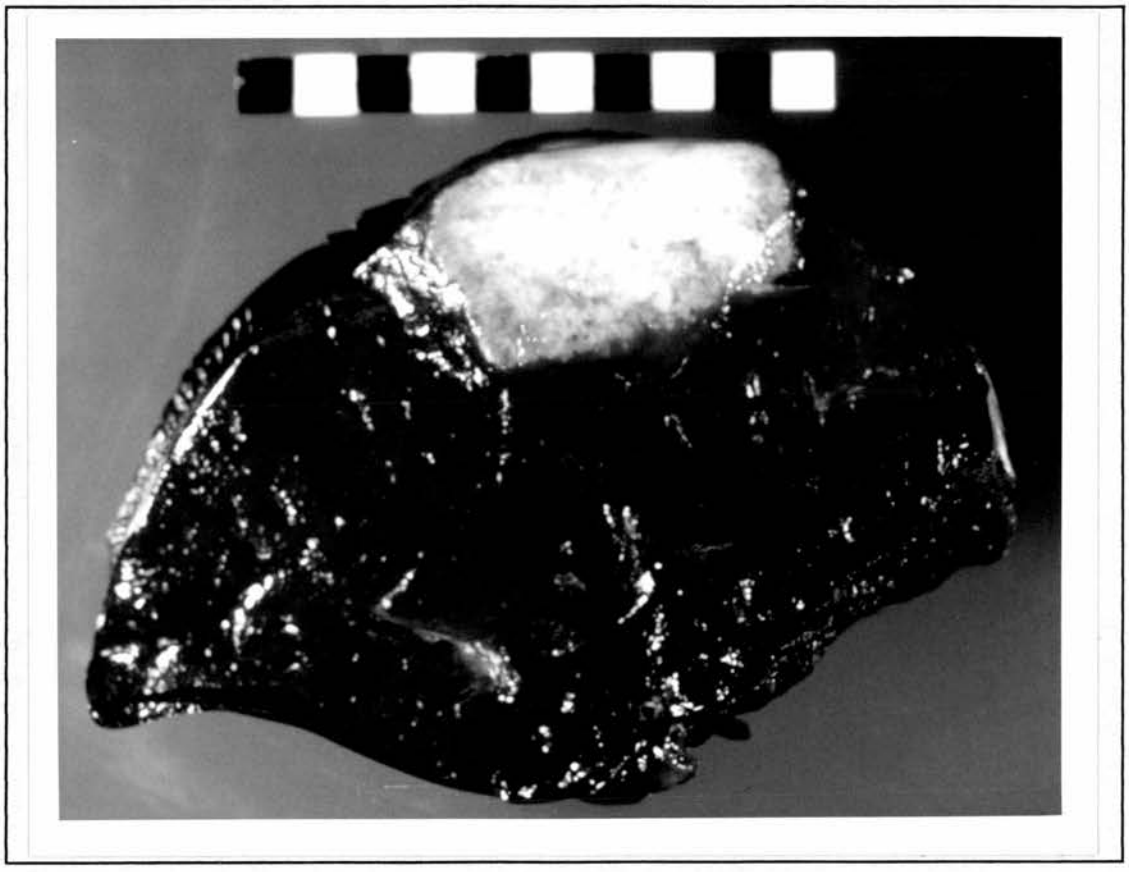

Plate 2. A large, solitary metastases detected by ultrasound, CT scanning and palpation prior to resection.

The site of implantation is not random either, rather it is a function of the number of cells (seeds) delivered to the target organ (soil) and the ability of that 'soil' to support the growth of the 'seeds'. The 'seed and soil' hypothesis is by no means new (Paget S, 1889) and has been supported by more recent research (Hart IR, 1981). Although the latter refers to experimental sarcoma cell lines, it has shown that the metastases show organ-specific implantation even when the tissue of the target organ is placed in a heterotopic site.
Further evidence against the hypothesis of metastatic implantation being merely

a function of the number of 'seeds' being delivered to a 'soil' may be derived from patients with malignant ascites. Peritoneal-venous shunts, allow patients with malignant ascites have their ascitic fluid drained internally to the great veins (Laveen shunts). This method of drainage delivers large numbers of tumour cells to the pulmonary capillary beds. Despite this there is not a marked increase in the number of pulmonary metastases associated with the use of these shunts (Tarin D, 1984). This suggests that the pulmonary capillary bed is not a fertile soil for malignant cells contained in the peritoneal fluid in these cases.

I.A.1.b. Detection and growth of metastases

A number of investigations have been directed towards the physical detection of hepatic metastases, the serological markers they produce, their specific cell surface antigens and the physiological and anatomical changes caused by their presence. Detection of the actual metastases at laparotomy, by visualisation and palpation, was until recently the "gold standard", despite strong evidence that palpation was insensitive (Schreve RH, 1984; Hogg L, 1955). Up to 29% of metastases present at the time of operation are not detected by palpation (Finlay IG, 1982). Longitudinal studies have shown that metastases missed by palpation will appear during follow-up, being detected by computerised axial tomography (CT) scanning (Finlay IG, 1982; Machi J, 1991).

Hepatic metastases may be of different sizes and appear at different times during follow-up (Plate 3.). If we assume that metastases from a single tumour all grow at approximately the same rate (Finlay IG, 1988), then the implication is that at the time of surgery the liver contains metastases at all stages of development. This also assumes that the establishment of one metastasis does not prejudice the development of another in the same organ. Also that metastatic tumours shed cells on numerous occasions or perhaps constantly and not as a single event.

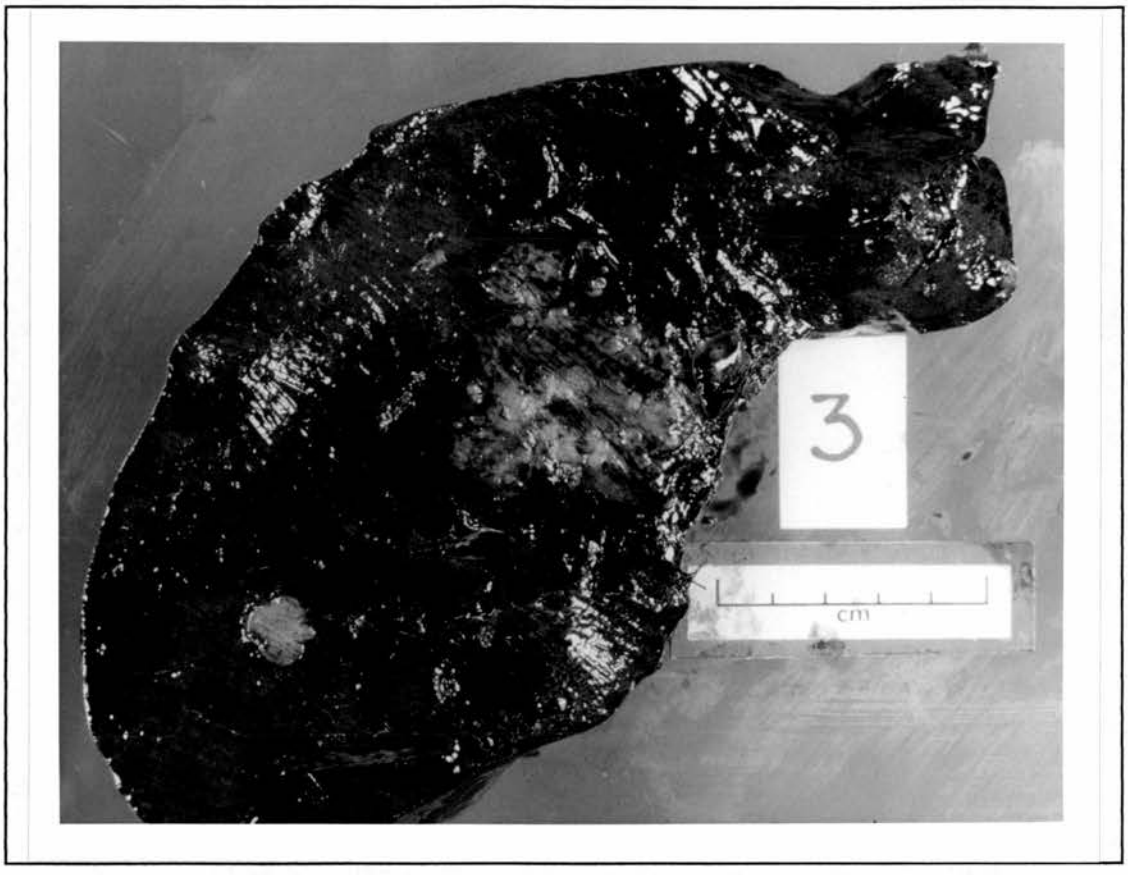

Plate 3. Multiple metastases in the resected right hemi liver, from a primary colorectal cancer. The small solitary nodule in the bottom left of the photograph is 1.2 cm in diameter and spherical in form.

Solitary metastases are rare and occur in only 10%-14% of patients (Blumgart L, 1982; Scheele J, 1991) with colorectal cancer. The finding of a truly solitary metastasis implies that only one cell or clump of cells successfully implanted and evaded destruction by the host immune system. However, apparently solitary metastases may actually be the only detectable metastases in a liver which harbours a number of other occult lesions. If the apparently solitary metastases is resected and the patient survives, without hepatic recurrence, then either it really was the only lesion, or the patient continues to harbour occult, hepatic, metastatic disease. This may become apparent, remain dormant or be completely eradicated by the host immune response. Between 70% and 75% of patients die following hepatic resection for metastases: in these patients micro metastases, occult at the time of resection, continue to grow, becoming clinically apparent within five years.

Resection of solitary or small numbers of hepatic metastases confers a survival

benefit of 25% - 30 % at five years (Adson MA, 1987). The finding of a resectable lesion occurs in 2-5% of patients and may suggests a level of immune competence towards the primary tumour in these patients. This presence of an active host defence may in itself confer a survival advantage.

It is not possible to predict who will survive after curative hepatic resection and who will not. It is recognised however, that the presence of residual disease: either as multiple micro metastases in the resected specimen or tumour at the resection margin, indicates a poor prognosis.

I.A.2. Magnitude of problem

I.A.2.a. Number of patients in Scotland and in Great Britain

There has been a progressive rise in the registration of colorectal cancer in Scotland from 2,594 in 1975 to 2,860 in 1986. This trend is similar for the rest of the country with 27,000 new cases registered annually in Great Britain. In Scotland the mortality rate for colorectal cancer has remained relatively constant at 35 per 100,000 population per annum. In Lothian, 426 patients underwent primary surgery for colorectal cancer in 1987 (Lothian Surgical Audit). Colorectal cancer was the registered cause of death for 253 patients in the same year (WHO Mortality statistics 1987).

The crude 5 year survival rates for patients undergoing potentially curative resection of colonic cancer is 47-69% (Wield U, 1985; Murray D, 1975; Turnbull RB(Jr), 1967). Between 15% and 35% of patients have hepatic metastases present at the time of their primary surgery of which 8% to 24% are occult (Olsen AK, 1990; Finlay IG, 1983). More than 70% of patients who die with colorectal cancer have liver metastases present at the time of death (Pestana C, 1964). Patients with hepatic metastases have a 0% to 20% 3 year survival, and negligible 5 year survival (Wagner JS, 1984; Arnaud JP, 1984; Cady B, 1970).

Population and incidence data suggest that, in Scotland, 57 to 142 patients per annum will have resectable metastases.

I.A.2.b. Mortality

There has been a decrease in the peri-operative mortality associated with colorectal cancer surgery over the past 50 years. Prior to the Second World War, peri-operative mortality was in the region of 11% to 31% with 41% to

50% operability rates (Allen AW, 1947; McKittrick LS, 1948; Grinnell RS, 1953; Morgan CN, 1957; Smiddy FG, 1957). This has improved with a decrease in peri-operative mortality to between 5% and 7% and an operability rate of 90% (Pihl E, 1980; Turunen MJ, 1983). Furthermore advances in anaesthetic and intensive care techniques plus the development of more effective antibiotics have led to a larger number of older and sicker patients being offered and surviving surgery. Although the 30 day post-operative mortality following colorectal surgery has improved, the long-term survival of patients is no better now than it was before the First World War. There has been no change in the death rates from the disease itself in over forty years (Wield U, 1985).

I.A.2.c. Change in the population in the same period

As the mean age of the population has risen so has the annual registration of patients with colorectal cancer. Over and above this there is a rise in the incidence of the colorectal cancer exceeding that expected from the increasing age of the population. That is, the number of cases of colon cancer per 100,000 patients over 70 years of age is increasing annually. There are also an increases in the number of right sided cancers (Green FL, 1983) and cancers in women (which may be related to the increase in smoking in women). It is not known how these changes will affect survival or the incidence of metastases in the next decade.

I.A.2.d. Variation with ethnic groups and environment

There is a marked difference in the incidence of colorectal cancer related to the ethnic origin of a community and the environment in which that group is placed. The incidence of colon cancer in Nigeria is around 2.5 : 100,000 compared to around 32 : 100,000 in Scotland (Waterhouse JAH, 1976). This difference is probably due to enviromental factors. There are also genetic factors within a population which affect the incidence of cancer (Lynch HT, 1981; Lovett E, 1976). Both environmental and genetic factors are disrupted by ethnic mixing and population movements. There are no published data examining the relationship of hepatic metastases to ethnic group or environment.

I.B. The history of surgery

I.B.1. Early surgery

Early rectal surgery was largely limited to the local resection of tumours described by Volkman in 1878. At the turn of the century Herbert Allingham performed local excision of rectal tumours by splitting the rectum and working from inside the lumen. The operation was by its design contaminating and the results were poor. Patients having these operations were left incontinent and tumour commonly recurred locally after a few months (Lockhart-Mummery JP, 1926). Kraskes' operation of trans-sacral resection of tumour and rectum left the patient with either a sacral anus or a re-anastomosis and was little better (Lockhart-Mummery JP, 1926). Attempts at re-anastomosis were generally poor; the inverting stitch described by Lambert in 1826 was first used successfully by Diffenbach in 1836 to re-anastomose bowel in dogs. The same technique was used in the colon following resection for cancer eight years later by Reybard of Lyon.

I.B.1.a. Colostomy

While the first description of a lumbar colostomy was published by Amussat in 1839 the operation was actually first performed in 1836. This was followed by an anterior abdominal wall colostomy described by Maydl in 1888. Although both of these procedures reduced post-operative deaths, mortality remained high. The double-barrel colostomy was independently described by Paul of Liverpool in 1895 and Von Mikulicz of Breslaw in 1903 and became popular. The procedure was, however, first described by Bloch in 1894 (Williams NS, 1993).

I.B.1.b. Abdominoperineal resection

A major advance in the surgery for rectal cancer came in 1908 with the description by Miles of the operation of abdominoperineal resection for rectal carcinoma (Miles EW, 1925). This operation along with description of the perineal excision of the rectum by Lockhart-Mummery in 1905 (Lockhart-Mummery JP, 1926) marked the beginning of modern surgery for carcinoma of the rectum. Until this time little attention had been paid to the staging of rectal cancers, the mortality of the surgery having been so high that there were very few patients who survived past 30 days to be studied. It is likely that the mortality from other illnesses prevalent at the turn of the century would also have had a considerable independent effect on survival.

In the Post War period there have been innumerable advances in both surgical and anaesthetic techniques and the general health of the population has improved. As more patients have survived the curative operative procedures for the treatment of colorectal cancer, their long-term outcome has been related to the extent of their disease at presentation and its amenity to treatment.

I.C. Staging

I.C.1. Why stage ?

It is possible to place patients into survival groups defined by the extent and the nature (stage) of their primary tumour. This staging aids: the clinician in the planning of treatment, gives some indication of prognosis, assists in the evaluation of treatment, facilitates the exchange of information between treatment centres and contributes to the continuing investigation of human cancers (Hermanek P, 1987).

I.C.1.a. History

As peri-operative mortality began to fall it became apparent that the extent of the tumour and the integrity of the resection could prejudice the survival of the patient. Lockhart-Mummery published the results of his first 200 cases of perineal resection in which he noted that prognosis was related to the depth of penetration of the tumour into or through the rectal wall. Survival for the first year was significantly higher in those patients in whom the tumour had not penetrated the muscularis mucosa (in this study he made no reference to hepatic spread of tumour) (1926). Rankin (Rankin FW, 1928) described the value of the grade of tumour as an indicator of prognosis. He found that as the degree of differentiation increased so did survival, with poorly differentiated (high grade) tumours having the worst prognosis.

Dukes emphasised the value of recording the local extent of tumours of the rectum in predicting outcome for rectal carcinoma (Dukes CE, 1932). Tumours were staged as : A, Disease confined to the rectal wall; B, Direct extension into extra rectal tissue (no lymphatic involvement); C, Extension with involvement of regional lymph nodes.

This classification did not take account of more distant, extra rectal spread.

I.C.1.b. Hepatic metastases

In 1928 F.W. Rankin wrote "Nowhere is there any dissension from the dictum that metastases to the liver rules out radical resection except.....as a palliative

measure." (Rankin FW, 1928). He had noted that patients with hepatic metastases, without exception, did not enjoy long-term survival. Dukes (1958) modified his classification to take account of the presence of tumour in the most proximal lymph node of the resected specimen, Dukes C2. A further addition, Dukes D, indicating distant spread of tumour outwith the resected specimen is now in common use.

The Dukes classification remains a standard method of reporting used by many pathologists. It is also generally accepted by colorectal surgeons as a practical and useful system of reporting for patients with colon and rectal cancer. The Dukes classification of rectal cancers and similar staging systems do not rely on any form of pre-operative data to aid in the prediction of long-term outcome. There are, however, a number of investigations that may be undertaken prior to surgery to indicate prognosis.

I.C.2. Current practice in staging of colorectal cancer

I.C.2.a. Accuracy of staging in applying prognostic groups to patients.

Dukes staging is used to place patients into groups of expected survival. Patients with Dukes A disease will have a 97% five year survival; Dukes B 77.6% , Dukes C1 40.9% , Dukes C2 13.6%.(Age sex corrected five year survival Dukes HE, 1958). These figures represent the mean survival for a patient placed in the group. Other features of the resected specimen may be used to try to give a more accurate estimation of outcome and these are considered below.

Number of positive nodes	**% 5 year survival**
1	63.6
2-5	36.1
6-10	21.9
more than 10	2.1

Fig 1. The number of lymph nodes involved is a negative prognostic indicator (Dukes HE, 1958)

The number of lymph nodes containing metastases is of significance, survival decreases as the number of lymph node metastases increases (*Fig 1.*). The site of lymphatic metastases in the resected specimen is also of importance. Tumours were originally staged as Dukes C if there was evidence of lymphatic

involvement. However, it is recognised that the involvement of the lymph node nearest to the ligature on the vascular pedicle (the apical node) of the resection specimen is a negative prognostic indicator. Dukes original stage "C" is refined to take account of this and is redefined as Dukes C1 and C2 if the apical node is involved.

Grade	% 5 year survival
Low	77.3
Average	60.6
High	28.9

Fig 2. Grade of tumour related to five year survival. (Dukes CE, 1958)

Involvement of the apical node (C2) gives a five year survival of 13.6% while sparing (C1) gives a figure of 40.9%. The overall survival for stage "C" patients is 32%. The degree of differentiation of the tumour is also significant and can be related to prognosis (*Fig 2.*). The grade of malignancy allows patients to be grouped in a similar manner to the extent of spread of tumour. Grade of malignancy is closely related to the degree of local invasion but gives additional information in terms of prognosis. It should also be noted that grade of tumour is related to age of patients, with significantly more high grade tumours occurring in younger rather than in older patients. This association is slightly stronger in women than men. These data relate to a specific method of treatment of the resected specimen and could not be immediately related to all surgical specimens. Also these data deal only with rectal cancer and not with colon cancer (Dukes CE, 1958).

Variable	Score		
	0	1	2
Limitation of growth to bowel wall	yes	no	
Lymph nodes involved	0	1-4	>4
Margin **E**xpanding/ **I**nfiltrating	**E**	**I**	
Peritumoural lymphocyte infiltrate	yes	no	

Fig 3. Jass score from 0 to 5 indicates prognosis for colorectal cancer (Jass JR, 1987).

There have been subsequent systems suggested for the staging of colorectal cancer: one of the more significant is from Jass et al (1987). Recognising the importance of being able to place patients accurately in prognostic groups Jass

et al. have attempted to improve upon the Dukes system. By reviewing the resection specimens from 379 operations performed between 1960 and 1965, pathological findings were related to known, actual survival. A number of discrete pathological variables were identified, each of which independently predicted survival. These variables were scored and weighted to give the best fit to the known outcome ("Jass" score).

This system gave a lowest possible score of 0 and a highest of 5 (*Fig 3.*). The scores were then grouped into stages: Stage I, score 0-1, Stage II, score 2, Stage III, score 3, Stage IV, score 4-5. Five year survival was then predicted for a group of 710 patients using the new system (*Fig 4.*). This scoring system placed 47% of patients in either very good I, or very poor IV, prognostic groups. Dukes staging of the same patients placed only 20.5% of patients into Dukes A, or C2. The "Jass" system gave a significant improvement in accuracy of prediction.

The "Jass" system relies on a subjective assessment of the infiltrating margin of the tumour and the degree of lymphocytic infiltration at the margin. In a separate study the investigators found little inter-operator variation when making these assessments (Jass JR, 1987). The counting of lymph nodes remains a labour intensive procedure but is included because of its additional independent value in this scoring system.

Stage	% 5 year survival	% patients in Group
I	94%	29%
II	83%	32%
III	56%	20%
IV	27%	18%

Fig 4. Jass score related to patients surviving 5 years. The score can be used to place 47% of patients into either very good or very poor prognostic groups (I or IV)

Michelassi et al have also described a 16 point staging system which is significantly more accurate than Dukes staging. It and others are not in common use because of their complexity (Michelassi F, 1991; Wolmark N, 1986; 1983; Whittaker M, 1976).

I.C.2.b. Change in recurrence rates with time over the past 50 years

There has been no evidence to suggest that the pattern of recurrence of colorectal cancer has changed over the past 50 years, despite changes in the

number and type of operations performed and in the suture materials used.

I.C.2.c. Limitations of pathological staging

The accuracy of the pathological staging systems is limited because they infer the extent of systemic disease from the evidence presented in the resected specimen. This leads to a number of errors; the piece of tumour which is fixed and stained is only a very small part of the whole; even if many sections are taken they still amount to a minute fraction of the entire mass of the tumour; only a very small fraction of the number of lymph nodes present will be detected; there may be microscopic foci of tumour spread outwith the resected specimen which are not seen and finally the tumour may not behave as its phenotype would suggest. It is unlikely that the current methods of assessment of tumour by its physical appearance will improve in their accuracy of determining outcome. Studies of the molecular biology of the tumours and their genetic makeup are more likely to give an accurate indication of which tumour could produce viable metastases and which could not. Until this technology is in place the only prospect of an improvement in the accuracy of staging is to detect a larger percentage of the metastases that are present at the time of operation.

The largest error in assessment of outcome for patients with colorectal cancer is the failure to detect hepatic metastases present at the time of operation (Finlay IG, 1982). The negative effect of the presence of hepatic metastases on survival is independent of local stage of disease. This powerful independent factor accounts for much of the inaccuracy of pathological staging systems in placing patients into a high survival group. It also confuses the outcome of trials of adjuvant treatment applied to patients who have had an apparently curative resection of their tumour. Up to 15% of these patients will in fact have hepatic disease. Such patients are unlikely to respond to adjuvant therapy designed to improve the survival following complete resection of all macroscopic disease.

I.C.3. Treatable metastases

I.C.3.a. Hepatic metastases

The importance of detection of hepatic metastases has increased because of their amenity to treatment. Successful resection of hepatic metastases increases expected survival from zero to 25% at 5 years (Adson MA, 1984,1987; Coppa GF, 1985; Blumgart LH, 1982; Fortner JG, 1984). Other treatments including

alcohol sclerotherapy, chemo-embolisation with cytotoxic drugs, cryotherapy and laser ablation have all been used to improve the quality of life by reducing rate of growth or reducing the size of tumours but have not shown any improvement in patient survival (Kemeny NM, 1985; Blumgart LH, 1982; Ravikumar TS, 1987; Charnley RM, 1990; Balch CM, 1987; Zhou X-D, 1988; Moffat FL, 1985; Goldberg JA, 1990). Chemo-embolisation has also been shown to reduce the levels of circulating carcinoembryonic antigen (CEA) in some patients (Yoshikawa C, 1987) and to reduce the symptoms in patients with metastases from carcinoid tumours. However, resection remains the only treatment to have shown a survival benefit.

I.C.3.b. Pulmonary metastases

There are very few data relating to the resection of pulmonary metastases from colorectal cancers. Resection confers a 21% chance of survival at 5 years with long-term survival related to the disease-free period prior to presentation (Kelm C, 1988). Pulmonary metastases occur late in the disease and are commonly associated with other dissemination, particularly hepatic metastases. There have been a number of cases where patients with resectable hepatic metastases and a single pulmonary metastasis have had both areas of disease resected. This is very uncommon (Brister SJ, 1988; Sugerbaker PH, 1990).

I.D. Pre-operative investigation of colorectal cancer patients

I.D.1. Introduction

Colorectal cancers present with alteration of bowel habit, blood in the stool, pain and weight loss. Pain, distension and obstruction may occur in advanced disease. None of these symptoms has been directly related to the presence or absence of hepatic metastases.

I.D.2. History

I.D.2.a. Personal history and presentation

The presenting history of colon cancer relates in the main to the presence of the primary tumour. It is uncommon to find a patient who presents with symptoms relating to the presence of hepatic metastases.

I.D.2.b. Family history

Although the genetic basis of colorectal cancer is currently the centre of much research there are no data linking early metastatic spread to any particular gene

addition / deletion. Nor has there been any familial link to the suceptability of an individual to hepatic metastases.

I.D.2.c. Signs

The signs relating to the presence of hepatic metastases occur late in the disease. The presence of a palpable malignant liver invariably means that the disease is beyond curative resection and may be beyond any form of treatment. Jaundice is also a late event in the course of hepatic metastases (McGarrity TJ, 1987).

I.E. Pre-operative investigation

I.E.1. Introduction

I.E.1.a. Pre-operative staging

Pre-operative assessment is undertaken prior to colonic surgery to ensure the eventual surgical intervention is to the patients best advantage. Between 4.5% and 9% of patients will have synchronous colonic tumours and up to 29% will have synchronous colonic polyps (Tate JJT, 1988) at the time of resection for their primary colorectal cancer. The investigation of patients presenting with colorectal cancer should include: barium enema, colonoscopy / sigmoidoscopy, postero-anterior chest radiograph, abdominal ultrasound scan of the liver, full blood count, serum urea and electrolytes, liver function tests (bilirubin, glutamine oxalic acid transaminase, glutamine pyruvic acid transaminase, lactate dehydrogenase, gamma-glutamyl transpeptidase, alkaline phosphatase) and blood estimation of the tumour marker Carcinoembryonic antigen (Wood CB, 1979; Schreve RH, 1984).

The most important findings are: the presence of more than one primary colonic tumour or the presence of a tumour and a number of polyps and the presence of metastatic tumour in liver, lung, bone or brain.

I.E.1.b. Barium enema

Barium enema examination has a sensitivity of 89% to 92% for colonic tumours and 72% for rectal cancers (Reiertsen O, 1987; Bolin S, 1988; Tate JJT, 1988).

I.E.1.c. Rigid sigmoidoscopy

Between 50% and 70% of colon and rectal cancers will be visualised by this means. The number of patients presenting with carcinomas that can be reached

by the sigmoidoscope is falling and the frequency of more proximal cancers is rising (Ghahremani G, 1989; Snyder DN, 1977; Rhodes JB, 1977; Maglinte DDT, 1983; Beart RW, 1983; Abrams JS, 1979; Greene FL, 1983).

I.E.1.d. Endoscopic sigmoidoscopy

The diagnostic accuracy of flexible endoscopy in the left side of the colon is high (90%) in the detection of polyps and cancers (Reiertsen O, 1987; Jensen J, 1990). The morbidity and mortality associated with the examination are low and are principally related to perforation of the colon and to hypoxia and hypotension related to the use of sedation.

I.E.1.e. Colonoscopy

Colonoscopy detects 90% of all cancers present at the time of the investigation if the investigation has been complete (Reiertsen O, 1987). In 30 % of cases the investigation is incomplete because of: inadequate preparation of the colon, failure to fully advance the instrument and operator error in failure to recognise incomplete advancement. The overall morbidity for colonoscopy is about 0.05% following polypectomy (Williams NS, 1993).

I.E.1.f. Chest radiography

It has been shown that pulmonary metastases are rare at the time of presentation (Sugarbaker PH, 1990) The plain postero-anterior chest radiograph will demonstrate these lesions. The detection rate is improved by the concomitant lateral views being taken. This investigation has a high resolution for metastases from colon cancer which can only be improved upon by thoracic CT scanning, which is not routinely used in the United Kingdom (Kelm C, 1988).

I.E.1.g. Ultrasonography of primary colorectal cancers

Trans-abdominal and endo-anal ultrasound may be used to stage not only the tumour but also local lymph nodes in the pelvis. Large carcinomas of greater than two centimetres diameter lying in an advantageous position in the colon may be detectable by 3.5Mhz trans-abdominal ultrasonography. Ultrasonography, however, lacks the sensitivity and specificity to be used as a diagnostic tool in the detection of impalpable primary colonic tumours. Endo-anal ultrasonography may be used to detect the depth of penetration of rectal cancers and the presence of pelvic lymph node involvement (Holdsworth PJ, 1988).

I.E.1.h. Computerised axial Tomography (CT)

CT of the pelvis may provide useful information as to the stage of known rectal and pelvic colonic cancers. CT scanning provides accurate information as to the local infiltration of the tumour in relation to the bony and vascular structures of the pelvis. CT scanning does not give sufficient detail of the rectal wall to be able to provide information regarding the depth of penetration of a cancer in relation to the muscularis propria and the muscularis mucosae. CT may detect local lymph node involvement and involvement of other pelvic organs. Pelvic CT scanning can be enhanced by the use of a dilute barium enema to increase the attenuation afforded by the rectal mucosa, and a vaginal tampon to indicate the position of the vaginal vault. Intravenous urography may be performed at the same time to increase the attenuation of the ureters and the urinary bladder. With this enhancement of the urinary tract it is possible to identify invasion or compression of the urinary tract (Freeney PC, 1986; Holdsworth PJ, 1988; Thompson WM, 1986).

I.E.1.i. Rectal examination

Attempts have been made to locally stage rectal cancers pre-operatively. Digital examination noting the size of the tumour and its fixity combined with sigmoidoscopic biopsy are related to outcome. The advent of endoluminal ultrasonography has improved the accuracy of local staging, particularly with regard to depth of penetration. High frequency (7.5Mhz) 360 degree probes and linear array (5-7.5Mhz) probes give visualisation of the muscle layers of the rectal wall. Tumour penetration can be related to these layers, the boundaries between the mucosa, muscularis and the adjacent fat giving strong echo reflections. Adjacent lymph nodes can be assessed, characteristic changes in the attenuation occurring as the node approaches 1cm in diameter and the degree of replacement by tumour approaches 50% (Holdsworth PJ, 1988).

I.F. Summary

There has been no change in the long-term outcome for patients with colorectal cancer in the last 50 years, although there has been an improvement in the peri-operative mortality associated with the primary surgery for colorectal cancer. There have been a number of attempts to improve upon Dukes staging, to put more patients into either 'very good' or 'very poor' prognostic groups. The Jass classification is better than Dukes in this regard but has not yet been widely accepted. It also fails to take account of the presence or absence of hepatic metastases.

Pre-operative investigation of patients with colorectal cancer now routinely involves visualisation of the entire colon to detect synchronous lesions and a chest X-ray to detect pulmonary metastases. Liver ultrasonography may also be undertaken. Following surgical resection, the specimen will be examined by a pathologist to confirm the diagnosis of colorectal cancer and to calculate the stage of the disease. This staging is then used to inform the patient of their prognosis, decide on further treatments, follow-up protocols, and to group patients with similar prognosis for research purposes.

Although there have been improvements in the pre-operative investigations to image the liver and an increasing awareness of the importance of the presence of hepatic metastases, little has been done to improve their peri-operative detection: 15% of patients still have occult hepatic metastases following their primary surgery. These patients have a mean survival of 18 months. Failure to take into account the presence of occult hepatic metastases introduces a random factor which radically affects outcome. Occult hepatic metastases may be the single most important determinant of outcome in patients undergoing curative primary resection of colorectal cancer.

Chapter II

Ultrasonography and the detection of hepatic metastases

II.A. The history of ultrasonography

II.A.1. Introduction

Discovery of the scientific basis of ultrasound precedes the discovery of X-rays. In 1880, fifteen years before the first X-ray plates were produced, Jacques and Piérre Curie (later to marry Marie Sklodow) discovered the piezoelectric effect. They found that when certain naturally occurring crystals were physically deformed, an electrical voltage was produced. Similarly if a voltage was passed across the crystal, a small change in its physical shape would occur. The application of an alternating current would allow sound waves to be produced at the frequency of the alternating current. This effect allowed ultra high frequency sound waves - outside the range of the human ear - to be produced. No further development of the possible applications of ultrasound took place until the first World War when Piérre Langevin developed a system to detect submarines by their reflection of pulsed sound waves in water. Sound Navigation and Ranging (SONAR) allowed the Royal Navy to detect and sink a great many of the German submarine fleet.

The second World War saw the further development of SONAR in the tracking of submarines and the development of smaller ultrasonic devices for industrial use. The need to detect flaws within mass produced steel, for the shipbuilding industry, led to the development of ultrasonic "flaw detectors". These devices beamed ultrasound waves through the steel and recorded their reflections off internal fissures, thus revealing otherwise unseen defects.

II.A.1.a. Medical ultrasonography

Following preliminary laboratory and animal work (Wild JJ, 1950; French LA, 1951) the first medical application of ultrasonography was in 1950 (French LA, 1950). A simple single crystal transducer was used to look at living tissues in an attempt to define structure (Wild JJ, 1952). These early images were unclear and difficult to interpret and further development of the

technique was delayed by the lack of appropriate technology. The advent of semiconductors and subsequently "micro chips " accelerated the development of ultrasonography.

II.A.2. Developments

Major developments in extra-corporal ultrasonography have been; M-mode and then B-mode scanning (Donald I, 1958), articulated arms and latterly sectoral scanners or linear array transducers to produce a sectional picture of the body's anatomy and the production of images from black to white in a number of graduations of grey. Each of these developments have improved the quality of the images obtained with a corresponding increase in the accuracy of the investigation. The most recent innovation in hepatic ultrasonography has been the introduction of probes that can be placed on the surface of the liver during surgery. This is known as intraoperative ultrasound scanning (IOUSS).

II.B. Scanning modes

II.B.1. A-mode scanning

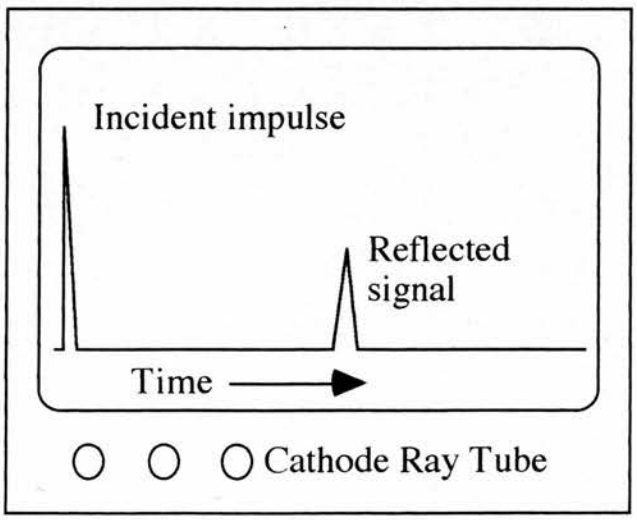

Fig 1. Cathode ray tube with incident and reflected signal. This represents the simplest form of ultrasound scanning. The time between the incident pulse and the returning signal is proportional to the distance from the transducer to the reflecting interface.

The earliest ultrasonographic images were the simple representation on a cathode ray tube (CRT) of the incident ultrasound signal and the returning signal as upward deflections of the baseline (*Fig 1.*), with the baseline sweep of the CRT being triggered by the incident pulse.

II.B.2. M-mode scanning

During M-mode scanning, the incident and reflected signals are represented as points of brightness along a vertical line. The incident signal appears at the top of screen and the reflected signal at a lower point. The distance between the points on the line is proportional to the distance of the point of reflection from the ultrasound probe. The early bi-stable machines gave images in black and white (*Fig 2.)* with no grey shades. The level at which a reflected signal was strong enough to produce an image could be varied by increasing or decreasing the sensitivity of the signal amplifier. This made very high contrast images which were difficult to interpret and unintelligible to the untrained eye.

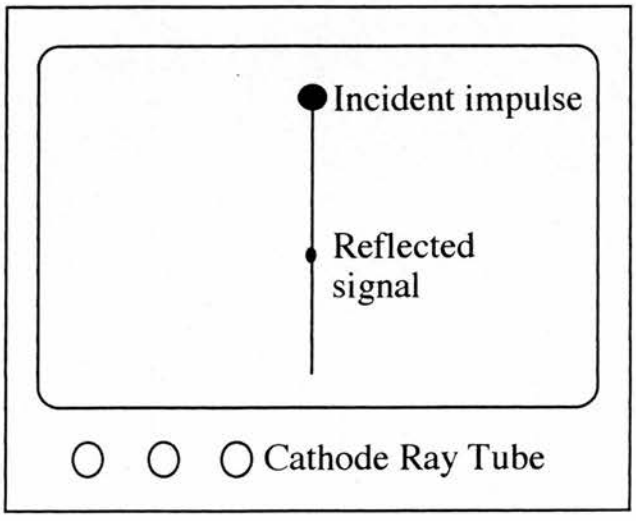

Fig 2. M-mode in vertical orientation, this output can be applied to a thermal printer to provide a permanent record of heart valve movement.

II.B.3. Real time B-mode scanning

M-mode ultrasound scanning allows the detection of movement but the images produced are not immediately recognisable as anatomical structures. However if the vertical line of the M-mode scan is made to pan through the tissues by either electronic or mechanical means, a true "picture" can be produced. A very large number of "M-mode" images are then displayed side by side giving a composite picture of the planes of reflection in the tissues under interrogation (*Fig 3*). The ultrasound images are acquired rapidly and refreshed at a rate of more than 15 times per second. The successive images appear to create a moving picture when in fact there is just a sequence of single frames. Flicker is virtually eliminated by having the previous line remain until it is overwritten by the subsequent line, unlike Cinema film where each entire image is seen and then replaced. This creates a smooth image and is an important factor in the reduction of operator fatigue.

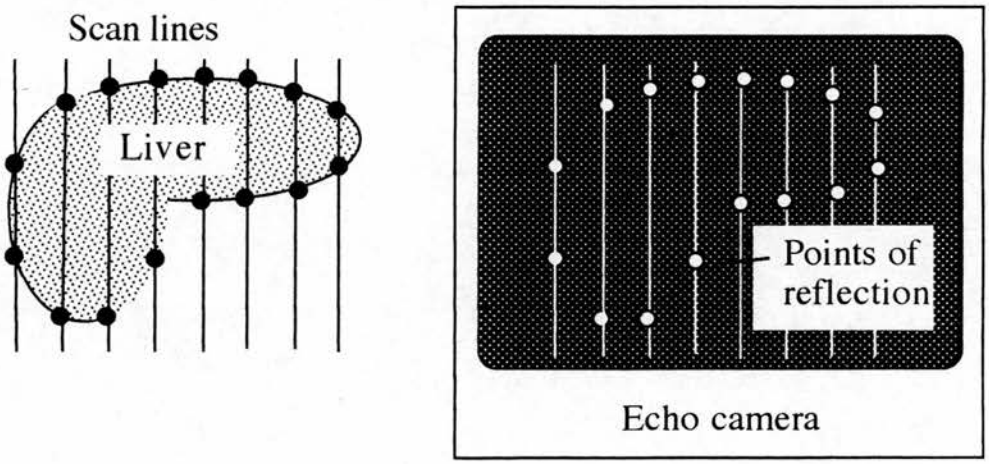

Fig 3. Multiple "M-mode" images side by side create an anatomically recognisable picture: a B-mode scan.

The returning ultrasound signal can be processed so that the intensity of the image on the screen is proportional to the intensity of the returning signal. Each strength of returning signal being represented as a shade of grey, the stronger the signal the lighter the shade. This creates a grey scale from which the image is constructed. Grey scale images in B-mode give true anatomical representations of the internal structures of the body in real time, with

movement. This is the type of system used for most general applications in ultrasound.

II.C. Physical principles of ultrasound

II.C.1. The piezoelectric effect

Ultrasound scanning relies on the physical properties of piezoelectric crystals. When an electric current is passed across the crystal it deforms. This change in shape is almost instantaneous and if the crystal is embedded in sound transmitting medium, then the change in shape of the crystal is transmitted to that medium as a pressure (sound) wave. Similarly if a physical force is applied to a piezoelectric crystal, an electric current is generated. The power generated is proportional to the extent of the deformity of the crystal.

When an alternating current is passed across the crystal, it will vibrate with the same frequency as, and with an amplitude proportional to, the voltage of the current. This vibration creates the sound. Once generated, the sound waves (areas of compression and rarefaction in the medium) are governed by the laws of wave physics. Ultrasound waves have the following properties;

a. They can be focused: refraction occurs as sound travels through materials of different densities. The speed of propagation of the waves increases in proportion to the density of the material. Thus a lens can be formed from a dense material to focus the waves.

b. They can be reflected: at any interface between two materials of different density a proportion of the incident sound wave will be reflected from the interface. Reflection is dependent on the degree of difference in the densities of the two materials creating the interface, their smoothness and the angle of incidence of the wave front to the interface. The direction of the reflection is dependent on the angle of the incident wave front to the interface. If the interface is irregular, then the wave front will be reflected in a great many directions (scattered). The most severe form of scatter is the reflection

of sound from a large number of points within a medium, such as red blood corpuscles within a blood vessel.

c. Sound waves undergo diffraction and interference. Diffraction occurs at the point of origin of the wave and after interaction with any obstacle in the wave path. The edge of the wave front is propagated more slowly than the centre and so the wave front becomes divergent. This phenomenon causes the sound wave to fill in the space behind obstacles. If two ultrasound beams cross each other they may interfere. This can occur between the incident and reflected part of the same beam. Interference occurs when an area of rarefaction and compression meet and cancel each other out. This can cause both the degradation of the image and the appearance of phantom images.

d. A proportion of the ultrasound beam is absorbed as it passes through tissues. The degree of absorption is dependent on a number of physical properties of the material but primarily on its coefficient of elasticity. The more elastic a material is, the less efficient is its transmission of sound. Efficiency of transmission is also related to density. As the density of the medium increases so does its efficiency of transmission of sound.

e. Attenuation is a summation of all factors which reduce the power of the ultrasound wave as it passes through a material. These factors are: absorption, reflection, scattering, refraction and wave front divergence. The more homogeneous a material is the less scatter, the fewer interfaces and the less reflection and refraction will be evident. Absorption is dependent on the coefficient of elasticity, density of the material and the frequency of the ultrasound beam. Taking all of these factors into account, pure fluids and solids give high levels of signal transmission, whereas gases and heterogeneous fluids give lower levels.

II.C.2. Intensity

In order to discuss attenuation of an ultrasound signal, the strength of the signal must be quantified. The intensity of the ultrasound beam may be defined as the rate of flow of energy through a unit of area perpendicular to the direction of the beam. There are a number of formulae which can be used to calculate the intensity of the beam. One of these is

$$I = 1/2\rho c\,(2\pi f)^2\,\chi o^2$$

Where I is the intensity of the signal, ρ is the density of the medium, f is the frequency of the ultrasound signal and χo is the particle displacement amplitude in the medium.

The total power of a scanner (W) may be expressed as the ultrasonic intensity (I) multiplied by the cross sectional area of the scanning field (cm^2).

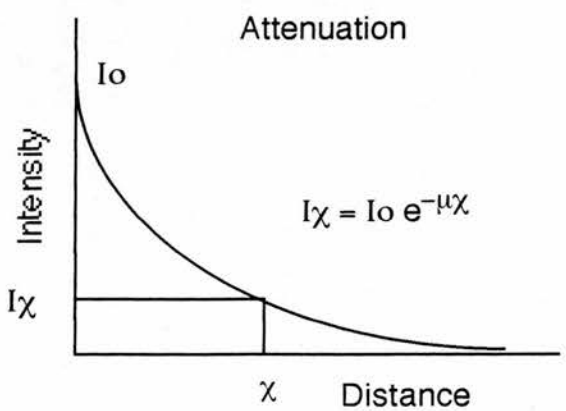

Fig 4 Intensity of an ultrasound signal I is attenuated as the distance X from the source increases where μ is the coefficient of attenuation (McDicken WN, 1991).

II.C.2.a. Coefficient of attenuation (μ)

The coefficient of attenuation (μ) can be calculated for any material by detecting the reduction in intensity of an ultrasound beam in the material. When Io is the intensity of the ultrasound beam at its origin, $I\chi$ is the intensity of the beam at distance χ from the origin and μ is the coefficient of attenuation *(Fig 4)*.

The coefficient of attenuation, μ, is the fraction of energy removed from a plane wave by attenuation in a unit path length and may be expressed in the following manner:

$$\mu = \frac{10}{\chi} \log\left(\frac{Io}{I\chi}\right)$$

This expression gives the coefficient of attenuation in dB/cm.

The attenuation coefficients for biological tissues have been calculated and tabulated (*Table 1*), these values are for a 1 MHz probe.

Tissue	Attenuation coefficient dB/cm
Blood	0.2
Muscle	1.5
Liver	0.7
Bone	10.0
Fat	0.6
Water	0.002 (absorption)
Soft tissue (average)	0.7

Table 1. Attenuation coefficients for biological tissues (McDicken WN, 1991) . The attenuation coefficient of muscle is high, the abdominal musculature causes significant attenuation during abdominal ultrasonography.

II.C.2.b. Time gain compensation

To minimise the effect of attenuation on the final image (*Fig 5*), the returning signals from distant interfaces are amplified to a greater degree than those in the near field.

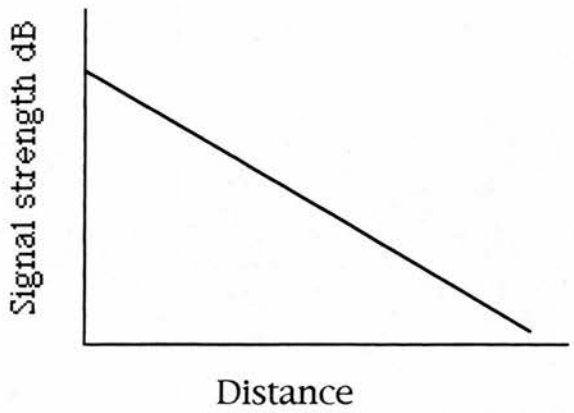

Fig 5. The returning signal strength in dB has a negative, linear relationship to the distance from the point of reflection. The slope is dependent on the attenuation coefficient of the tissues.

As the distance travelled is proportional to the time taken, the level of amplification is related to the time for the signal to return. There are a number of terms which relate to the enhancement of an ultrasound signal with time. Some of these are: swept-gain, depth-gain compensation, time-gain control and near- and far-gain control. All of these terms refer to the increasing amplification, with time, of the current produced by the returning ultrasound waves. The attenuation of a signal is calculated as $2d\mu$ when d is the distance from the ultrasound probe to the point of reflection and μ is the coefficient of attenuation. The time for the signal to return is related to the distance it has travelled. The speed of sound in soft tissue can be approximated as 1540m/s, and so the time for the signal to return from any

point can be calculated. Increasing amplification of the returning signal with time maintains a near constant image intensity on the screen. The level and delay of the gain can be altered to produce the best image in any given circumstance *(Fig 6)* .

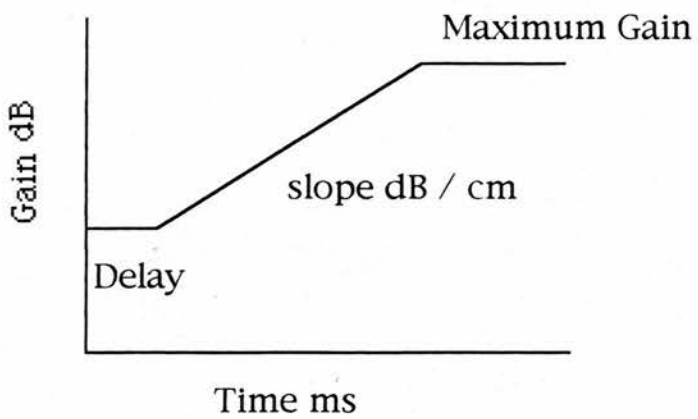

Fig 6 The gain applied to the returning signal is increased with time until a pre-set maximum gain is reached. The time is measured in milli-seconds (ms)

II.D. Biological images

II.D.1. Tissue differentiation

In early experiments, (French LA, 1951) showed that pulsed ultrasound waves at a power and frequency sufficient to produce an image did not produce harmful effects on the tissues. These images could be used to differentiate between tissues, the reflected signal being displayed as a peak on a CRT. In the same year Howry showed that tumours could be of sufficiently different acoustic impedance so as to produce a detectable reflection of ultrasonic waves at the interface of tumour and normal tissue (Howry DH,

1951). Later this effect was used to produce bi-phasic pictures of intra-abdominal masses (Donald I, 1958). The first images produced were on an oscilloscope showing the incident ultrasonic pulse and the delay in milliseconds to the reception of a reflection, a simple A-mode scan. By calibration and by a knowledge of the speed of sound in the soft tissue being investigated, it was possible to calculate the distance from the probe to the interface. Donald used pulsed beams of 2.5 MHz and 5 MHz. As the frequency of the pulsed beam was increased, the attenuation of the beam increased and so the range decreased. Reid and Wild had also noted the attenuation of the beam with distance and introduced time varied sensitivity (Time Gain Compensation, TGC) to enhance the returning signal (Wild JJ, 1952).

A-mode presentation was used to investigate the movements of the right atrium, the representation of the amplitude of the returning wave form being the brilliance of a point on the CRT. The scanning of that image across the screen gave the earliest M-mode scans (Donald I, 1958). Using a mechanical arm to link the time-base sweep of the oscilloscope to the movement of the probe, it was possible to build up composite pictures of a target (B-mode images). Donald was somewhat sceptical of the ability of the then currently available systems to differentiate between malignant and non malignant tissues as had been suggested by Wild (1952).

II.D.2. Key developments

In the decades since the early discovery of ultrasonography there have been a number of key developments. The general improvement in the fidelity of electronic components has led to an increase in the clarity of the images that can be produced. A decrease in the physical size of the machines has been brought about by the use of solid state components and the boom in micro computing has allowed the incorporation of more features into smaller and cheaper machines. It is now common to have probes which function at a spread of frequencies within a narrow band, allowing an improvement in near field resolution whilst maintaining depth penetration. A number of machines have dynamic focusing which allows the focal length of the beam to be altered during the scan to improve the definition of targets in either the near or far field. Waterproof probes which can be sterilised have been developed for intraoperative use. These are available in a number of formats from various

manufacturers. All of these probes have the advantage of small size and the ability to be introduced into the abdominal cavity.

Doppler shift scanners, incorporating both a standard and a Doppler image have been developed. The Doppler image is produced by detecting a shift in the frequency of a reflected ultrasound beam. The shift is caused by movement of the reflecting interface towards or away from the probes surface. The frequency shift is usually represented in colour on the screen and by an audio signal. A colour image is overlaid electronically on the standard display. By manipulation of the colour assigned to each frequency shift it is possible to differentiate both the direction and velocity of flow in a vessel. It is also possible to estimate the volume of flow in a vessel by measuring its cross sectional area and the velocity of the flow. Improvements in the fidelity of electrical components, electronic enhancement of the picture and better beam focusing have made ultrasound images easier to interpret. Component size has been reduced, allowing the construction of small linear arrays which may be mounted on endo-anal probes or laparoscopic probes. Intraoperative scanning heads are now of a convenient size for routine use.

II.E. Intraoperative ultrasound scanning (IOUSS)

II.E.1. Contact hepatic ultrasonography

Intraoperative hepatic ultrasound scanning removes the limitations of attenuation and access. As there is no tissue interposed between the scanning head and the capsule of the liver, the ultrasound signal is not attenuated or diffused and so image intensity and clarity are maintained. Access to the surface of the liver is practically unlimited: by dividing the triangular and coronary ligaments, the probe can be placed anywhere on the upper or lower surface of the liver (Plate 1). The reduction in attenuation allows the use of higher frequency probes which have lower penetration but better definition. These probes may also be placed directly onto the surface of the pancreas, biliary tree, kidneys, bladder and uterus. The most common use of intraoperative ultrasonography has been in the detection of hepatic tumours, pancreatic tumours and biliary calculi.

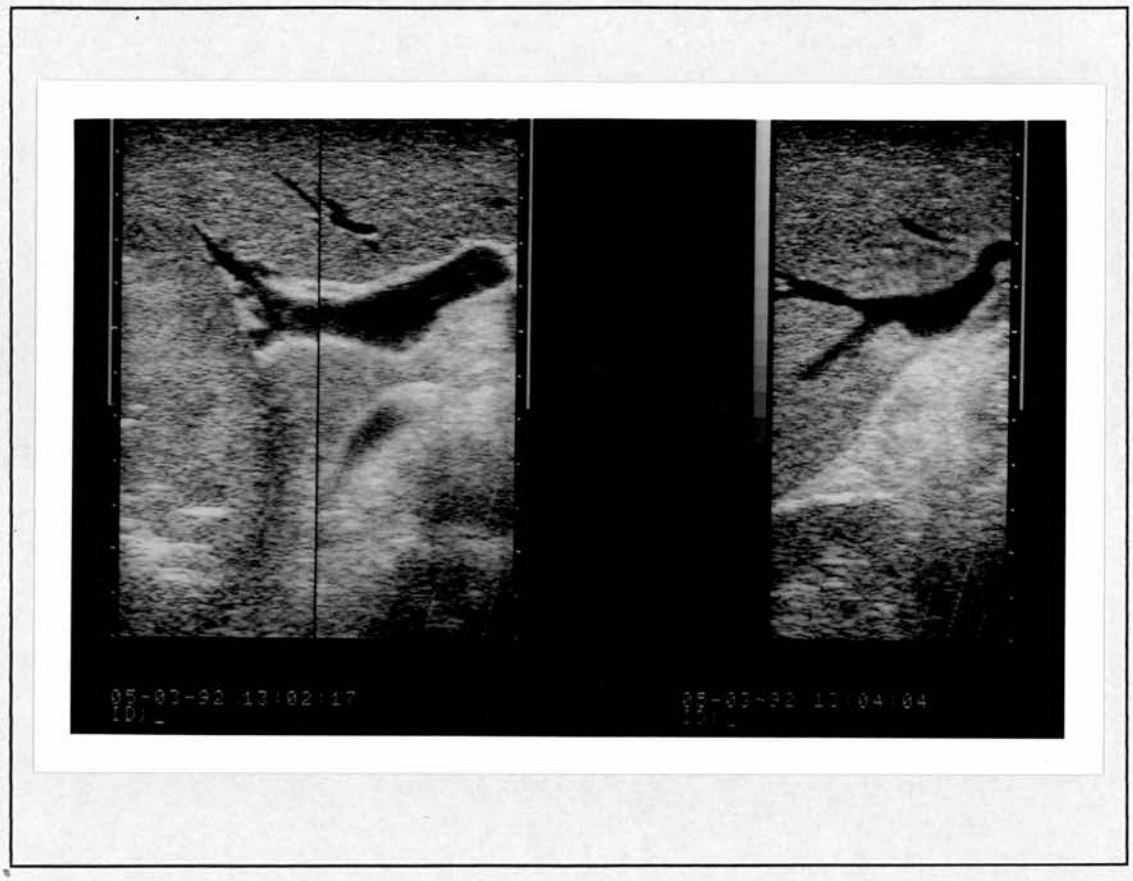

Plate 1. A composite intraoperative ultrasound scan of the portal confluence and a large tumour in the right liver.

II.E.1.a. Reduction in attenuation

Contact ultrasonography involves the use of a special ultrasound probe, for the direct examination of an organ or area of the body, during an operation. The probe is usually brought into direct contact with the organ to be examined, though in some cases an echo-lucent "stand off" may be used to reduce near field loss (see below). The organ may be viewed through a pool of sterile saline introduced into the body cavity. Direct contact or sono-lucent linkage between the scanning probe and the tissue to be imaged eliminates attenuation of the ultrasound signal by interposed structures. In particular, the sometimes thick layers of fat and muscle which lie between the surface of the skin and the target organ are avoided.

Fat has an acoustic attenuation coefficient of 0.6 dB/cm at 1MHz nearly equal to that of the liver (0.7 dB/cm), the attenuation by muscle is twice as great at 1.5 dB/cm. Scanning the liver through the anterior abdominal wall with 2 cm of subcutaneous fat and 2 cm of muscle reduces the effective depth of signal penetration into the liver by 6 cm i.e. 50% of the thickness of the organ. The signal has to travel the same path on its return and attenuation also applies. So interposition of 4 cm of subcutaneous tissue reduces the effective depth of visualisation of the liver by 12 cm. The attenuation coefficient gives a numerical value to the reduction in power of the ultrasound signal but does not quantify the loss of image clarity which also occurs. At each interface between tissue planes not only is the power of the signal reduced but also the integrity of the wave front. The effect is similar to looking through a series of plates of frosted glass. The focus of the beam is disrupted and the clarity of the reflected signal is lost. This loss of clarity does not have a numerical value.

Access to the liver is limited during preoperative ultrasonography. Because the liver is in contact with the diaphragm only a small part of its surface can be "seen" by a probe on the anterior abdominal wall, the remainder is hidden from view by the interposed, air-filled lung. It is sometimes possible to "see" the liver by scanning between the lower ribs through the acoustic window provided by the lower intercostal spaces, but again access is severely limited. This means that some areas of the liver always remain at a distance from the scanning head, in particular the posterior part of the right lobe, segments VII and VIII.

II.E.1.b. Loss of near field image

With all ultrasound probes there is an area of tissue immediately adjacent to the surface of the probe from which no image can be obtained. This occurs because of the design limitations of using the same crystals to both generate and detect the ultrasound waves. A 5 MHz probe produces sound waves in intermittent bursts at a rate of 20 - 30 Hz, this is referred to as the frame rate. Each of these pulses lasts for 0.025 to 0.016 of a second. The period of emission is greater than the time taken for the reflected signal from the tissues nearest to the probe face to return. As signals from the very near field cannot be received until emission has ceased, they are lost. The depth of tissue affected by this phenomenon depends largely on the design of the equipment and the duration of the pulse. In the case of the 5Mhz probe used in the study

the depth of loss has been measured at 4 mm by experiment (*Fig 7*). This loss of the near field can be overcome by placing a piece of acoustically transparent material, of greater thickness than the depth of near field loss, between the probe and the surface of the organ to be scanned. This is called a stand-off, and in practice a sterile condom filled with water is often used. The stand-off causes a marginal reduction in penetration.

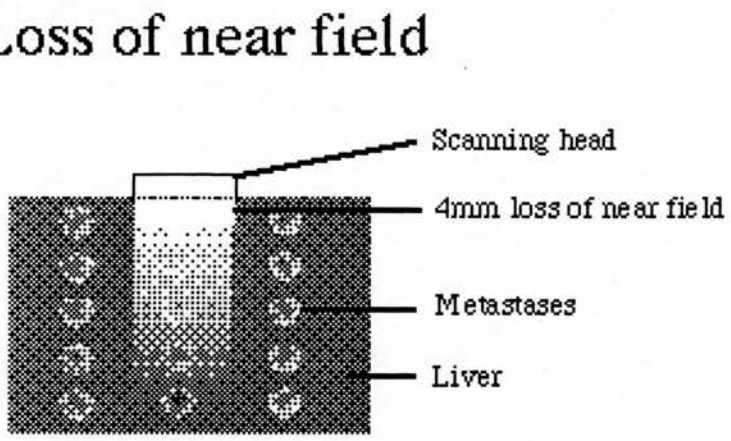

Fig 7 There may be no image from the near field because of interference between the emitted and received signal and because the transducer cannot receive the returning signal while it is still transmitting.

II.E.1.c. Development

Intraoperative ultrasonography has been used to detect biliary calculi (Hill MJ, 1961). Using a 2.5 MHz probe, experiments were performed in saline tanks, or with saline in the abdominal cavity to provide acoustic coupling. With stones of differing composition and size (from 3 to 30 mm). Hill et al were able to detect 3 mm stones in the test tank and 6 mm stones in the bile duct of patients. Similar research had shown that IOUSS could detect renal calculi (Schlegel JU, 1961). Research continued in the early 60's, using a 2.5 MHz industrial flaw detector modified for intraoperative use, which was able to detect 1 mm biliary calculi in water at a distance of 10 cm (Knight PR, 1963). Two stones could be differentiated if they were separated by 1 mm or more. The image was unaffected by the composition of the stones, however the angle of the probe to the face of the stone greatly affected the amplitude of the

reflected signal. During clinical trials, the probe detected stones in the common bile ducts in 3 out of 8 patients. The presence of stones was confirmed in these 3 patients by exploration and refuted, by cholangiography, in the remaining 5. This gave 100% accuracy for the scanner in the determination of stones in the common bile duct. Stones in the gallbladder were also detected, with ease, when present. All of these scans were performed in A-Mode and without "Kocherisation" of the duodenum.

In a larger series of 46 patients, Eiseman reported the use of two types of probe, the first a 2.25 MHz probe previously used to measure intra-cranial shift, the second a custom made miniature 7.5 MHz scanning head mounted on the end of a malleable common duct probe (Eiseman B, 1965). The 7.5 MHz probe was designed to be introduced directly into the common bile duct to look for stones during duct exploration. In 38 cases the large probe alone was used: there was 100% concordance in the detection of stones in the gallbladder by ultrasonography and the findings after its surgical removal. In 26 patients there were no stones in the common duct by operative cholangiography. This was confirmed in 24 patients by the small ultrasound probe. In the remaining two the small probe gave a false positive result, the first was the detection of a calcified lymph node behind the bile duct which was reported as a stone, and the second, calcification in the head of the pancreas was reported as a stone in the duct. Eighteen patients had stones in the common duct, 16 of these were detected by the larger 2.25 MHz probe. Eight patients, known to have stones in the duct, all had positive results when examined using the small probe. The authors felt that the accuracy of the investigation was dependent on the experience of the investigator.

II.E.1.d. Cholelithiasis

IOUSS has not become a popular method of assessing the presence of gallstones in the biliary tree, and its use by the general surgeon has never been high. Although IOUSS may be as accurate as intraoperative cholangiography (Sigel B, 1983; Lane RJ, 1982), cholangiography has the advantage of being simple to perform with little training needed to interpret the images. The same is not true of IOUSS. The capital costs of IOUSS are also high and may be prohibitive

II.E.1.e. Hepatic scanning

Early reports suggested that IOUSS could demonstrate small (5mm diameter) tumours within the liver (Plainfosse MC, 1983). With development in France and America, IOUSS has become a routine procedure during hepatic surgery. Hepatic resection is guided by the intrahepatic vascular anatomy (Bismuth H, 1987). The need for accurate information regarding the presence of vascular anomalies, coupled to a need for accurate information regarding the exact extent and vascular relationships of a tumour, have led to the rapid development of IOUSS by hepatic surgeons. The common intrahepatic ultrasonographic patterns of vascular anatomy (Castaing D, 1985) have been published, and provide a "map" for the operator. Hepatic resection for tumour is now a common operation and is guided in most cases by the use of IOUSS (Sheu J-C, 1984; 1985; Gozzetti G, 1986; Igawa S, 1985; Sugarbaker PH, 1990). IOUSS alters the course of the operation in up to 49% of cases (Rifkin MD, 1987; Parker GA, 1989) and may be used to direct the extent of resection during the operation.

It has been suggested that IOUSS of the liver is 99% sensitive in the detection of hepatomas (Makuuchi M, 1987). Boldrini has shown that IOUSS can be used at the time of resection of primary colorectal cancers to detect hepatic metastases with greater sensitivity than preoperative CT scanning, detecting tumour in 21 out of 86 patients compared to 16 out of 86 by CT scanning (Boldrini G, 1987). When used to detect hepatic metastases from colon cancer in 189 patients IOUSS has a reported sensitivity (at the time of operation) of 93.3%, specificity of 94%, a positive predictive value of 92.4%, a negative predictive value of 95% and an overall accuracy of 94.1% (Machi J, 1991). After follow-up of more than 18 months in all patients lesions missed by IOUSS became apparent and the results were re-evaluated (*Table 2 and 3*). Olsen in a series of 213 patients compared IOUSS to palpation and inspection at the time of operation. Sixty three patients were found to have metastases, 42 detected by preoperative ultrasonography or palpation at operation. The remaining 21 were detected by IOUSS, giving a sensitivity of 66.1% for palpation and 98.3% for IOUSS (Olsen AK, 1990). In a series of 54 patients being assessed prior to hepatic resection for neoplasm, compared IOUSS with CT, preoperative ultrasonography (USS) and angiography. IOUSS detected 167 lesions in 54 patients, preoperative USS detected 127 of these (76% accuracy) CT scanning in 48 patients detected 91 of 150 lesions present on IOUSS (60.6% accuracy) (Clarke MP,

1989). IOUSS is therefore a sensitive and accurate investigation in the detection of intrahepatic malignancy.

	Preop USS	**CT**	**Palpation**	**IOUSS**	**p-value**
True positive	43	49	69	97	
True negative	147	143	136	144	
False positive	5	9	16	8	
False negative	61	55	35	7	
Sensitivity (%)	41.3	47.1	66.3	93.3	p<0.0001
Specificity	96.7	94.1	89.5	94.7	
PPV	89.6	84.5	81.2	92.4	p<0.05
NPV	70.7	72.2	79.5	95.4	p<0.0001
Accuracy	74.2	75.0	80.1	94.1	p<0.0001

Table 2. Comparison of IOUSS, palpation, CT scanning and preoperative ultrasonography in the detection of hepatic metastases form colorectal cancer. The p value for the PPV represents IOUSS compared to palpation, the other p values are compared to all of the other investigations. Chi sq analysis was used (from Machi J, 1991).

	Preop USS	**CT**	**Palpation**	**IOUSS**	**p-value**
True positive	43	48	68	93	
True negative	141	136	129	134	
False positive	5	10	17	12	
False negative	70	65	45	20	
Sensitivity (%)	38.1	42.8	60.2	82.3	p<0.0005
Specificity	96.6	93.2	88.4	91.8	
PPV	89.6	82.8	80.0	88.6	
NPV	66.8	67.7	74.1	87.0	p<0.005
Accuracy	71.0	71.0	76.1	87.6	p<0.001

Table 3. After 18 months follow-up by CT and ultrasonography 188 patients were re-evaluated. Thirteen of 144 patients who had no evidence of metastases at the time of operation developed metastases in follow-up. On the basis of this information the results were recalculated (from Machi J, 1991).

II.F. Comparison of the methods of detection of hepatic tumours

II.F.1. Pre-operative assessment

II.F.1.a. Introduction

Whilst the intraoperative detection of hepatic tumours may be facilitated by ultrasonography, most patients with intra-hepatic malignancy will never undergo laparotomy. The majority of tumours are detected and delineated by pre-operative investigations. Each of these investigations has a recognised lower limit of resolution and overall accuracy. This must be taken into account when interpreting the results of the investigations.

The detection of the actual metastasis or tumour relies on there being a demonstrable difference between its composition and that of the surrounding liver. The physical presence of a tumour may be implied by a detectable displacement of other structures. Imaging techniques rely on these factors to identify tumours. The routine investigations in use at present are: hepatic scintigraphy, hepatic ultrasound, hepatic CT and hepatic arteriography.

II.F.2. Hepatic scintigraphy

Scintigraphy is the least specific and the least sensitive imaging technique (Schreve RH, 1984; Smith TJ, 1982, Alderson PO, 1983). The lower limit of resolution for scintigraphy is of the order of 2 cm depending on the site of the tumour. This poses difficulty in the assessment of the liver since up to 30% of hepatic metastases are smaller than 2 cm in diameter at presentation (Ozarda A, 1962).

Scintigraphy relies on the differential distribution of radioactive sulphur colloid, technetium 99m, within the liver. The colloid is scavenged from the circulation by Kupffer cells and held within these cells for a period of time. The photon emission of the colloid can then be detected by a gamma camera. The definition of a scintigram can be improved by attempting to label the tumour with a different isotope and then digitally subtracting the image of the tumour from that of the liver. External subtraction imaging using sheep IgG (radio labelled with I131) raised to carcinoembryonic antigen, with 99mTc-pertechnate and 99mTc-human serum albumin to identify tissue spaces, was used by Dykes. In 13 patients, 4 of 5 primary tumours and 8 of 11 secondary

sites of tumour were identified. One very large liver metastasis was not imaged and the size of the other tumours that were successfully imaged is not given. The anti-serum used was purified by immunoadsorption and produced fever in only one patient. Because of sensitisation of the patients to the serum, the examination could not be repeated. The IgG was raised against a CEA producing liver metastasis which may explain why the sheep IgG did not all bind to the free CEA in the circulation. A fall in the circulating CEA was noted in some patients and may have represented a proportion of the sheep IgG binding to free CEA. This type of subtraction scintigraphy is not currently in clinical use because the potential risk of patients becoming sensitised to the sheep IgG (Dykes PW,1980).

II.F.2.a. Scintigraphy, CT scanning and ultrasonography

A prospective comparison of scintigraphy, CT scanning and pre-operative ultrasonography (USS) in a group of 189 patients with breast or colon cancer, (Alderson PO, 1983) showed that, in patients who had all three investigations (n=122), CT scanning had a sensitivity of 93%, compared to 86% for scintigraphy and 82% for ultrasonography. The specificities for each of three investigations were not statistically different, although overall, CT scanning was the most accurate investigation. In comparing CT scanning and USS scanning Alderson showed little difference in the detection rate for each technique. In 25 patients, the final diagnosis of hepatic metastases was made on the basis of hepatic imaging, supported by the presence of extra hepatic lesions. These 25 patients did not have laparotomy to confirm the presence of hepatic lesions. There was no significant difference in the overall accuracy of the different investigations and there was no significant difference in the results for the patients who had operative confirmation of metastases and those who did not.

A study using bi-manual palpation at the time of surgery as the gold standard, found that scintigraphy at 15 minutes after injection of 185MBq of 99m Tc-Sn-colloid using four views gave an accuracy of 79% when compared to the operative findings (Schreve RH, 1984). This was not significantly different from pre-operative ultrasonography using a 3.5 MHz probe taking two views; supine and left lateral, or CT scanning with a Philips 300 scanner using a slice thickness of 1.2 cm at 1 cm intervals. The CT scans were enhanced using 500 ml of oral 3% iothalamate (380 mg I/ml) and 60 ml of intravenous iothalamate in all cases, except those with unequivocal liver involvement.

Scintigraphy was insensitive in the detection of small metastases and identified only 2:10 of those which were less than 2 cm in diameter. CT scanning detected 5:10 metastases of the same size. This study included patients with metastases from a number of different primary tumours (37 oesophagus, 27 gastric, 3 duodenum, 20 pancreatic or peri-pancreatic, and 26 colon). It is impossible to tell from the data if metastases from one primary site were more or less easy to detect than metastases from another primary site. The detection rate for scintigraphy in this study is high. As palpation at operation was used as the gold standard it is likely that a number of metastases present at operation were not detected. Scintigraphy detected 79% of palpable metastases as opposed to 79% of all metastases present.

II.F.2.b. Radioimmunoguided surgery

Scintigraphy has fallen behind CT scanning and ultrasonography as the investigation of choice in the detection of hepatic metastases. There has, however, been increasing interest in the use of radio-labelled antibodies to improve the performance of scintigraphy in the detection of metastases at operation (Abdel-Nabi HH, 1990). This study used indium-111-labelled antimucin murine antibody (MoAb) CCR086 in 17 patients with known metastases from colorectal carcinoma. A dose of 203.5 MBq of In-111 bound to 1 mg of CCR086 was co-infused with either 4 mg or 19 mg of unlabelled CCR086. All of the patients had histological confirmation of colorectal cancer and of at least one metastasis of 1 cm diameter. All had been discontinued from chemo- or immunotherapy for at least a week before the scan. Five of the patients also had a routine sulphur-colloid liver spleen scan performed. The results of the In-111 CCR086 scans were read with full knowledge of all other scans and the operative findings. The MoAb was shown to accumulate in 17 of 25 known lesions. The smallest identifiable liver lesion was 1.5 cm in diameter. A further 4 areas of uptake not previously suspected as being metastases were found but only 2 of these were confirmed on CT scanning. Of 12 patients with liver metastases, only 4 had hot spots in the liver on In-111 CCR086 scanning, a further 4 patients had mixed areas of uptake in metastases and the remainder had no uptake in the metastases.

A refinement of the use of radio labelled antibodies is radioimmunoguided surgery (RIGS) (Sardi A, 1989). The radio-labelled antibodies used were MoAbs B72.3 and 17-1A prepared by hybridoma technology. A hand-held

intraoperative gamma detection probe (GDP) (Neoprobe, Colombus, Ohio) was used to detect areas of localisation of the labelled antibody.

II.F.3. Preoperative ultrasonography and preoperative CT scanning of the liver

Ultrasonography is the mainstay clinical examination of the liver for the presence of metastases from colorectal cancer. With the advance of technology, the accuracy and sensitivity of ultrasonography has increased.

Schreve found ultrasonography to be as accurate as CT in the detection of hepatic metastases with a sensitivity of 85 % (Schreve RH, 1984). In a prospective audit of pre-operative investigations in patients with known hepatic metastases, Gunven was also able to demonstrate the comparative accuracy of CT scanning and ultrasonography. In 31 patients, 19 of whom had hepatic metastases from colorectal cancer, 26 had CT scans and 26 had ultrasonography performed. All of these patients went on to have laparotomy and IOUSS performed. Preoperative ultrasonography was performed using a 3.5 MHz linear array probe and a B-mode grey scale echo camera. A total of 113 metastases were detected by intraoperative scanning palpation and pathological sectioning . In this study the anatomical site of a metastasis did not appear to affect its likelihood of being detected by CT scanning. Preoperative ultrasonography was significantly less sensitive ($p < 0.05$) than CT scanning in the detection of lesions in the posterior part of the right lobe, missing 3 out of 5 lesions greater then 2 cm in diameter. Overall, of the metastases exposed to pre-operative ultrasound scanning, 75% were detected and 60% were correctly sited. Broken down by size, pre-operative ultrasonography detected only 9% of lesions smaller than 1 cm, 40% of lesions 1-2 cm in diameter and 89% of lesions greater than 2 cm. In this study, ultrasonography was less sensitive in the detection of metastases than CT scanning but of equal accuracy in the anatomical siting of the lesions detected (Gunven P, 1985).

A retrospective study of 108 patients, 63 of whom had hepatic malignant disease (McGarrity TJ, 1987), failed to support these findings. Only patients with a positive histological diagnosis were included and all ultrasonographic examinations were carried out with 2.5, 3.5, 5, or 7.5 MHz probes and real time B-mode grey scale echo cameras. The ultrasonographic scans of 61

patients were included in the analysis and compared to their histological findings. Ultrasonography had a sensitivity of 73% compared to 81% for CT scanning with a specificity of 94% compared to 83% and an accuracy of 84% compared to 82%. In conclusion, this study found that a negative ultrasonogram combined with a normal level of serum alkaline phosphatase was 100% specific for the absence of malignant disease, although this combination of results was only present in 11 (10%) of the patients studied.

In a prospective evaluation of CT scanning angiography and ultrasonography in 54 patients, Clarke found that ultrasonography detected more lesions than CT scanning (Clarke MP, 1989). All of the patients went on to have IOUSS which was used as the gold standard. Preoperative ultrasonography was performed on all patients and detected 76% of the total number of metastases. CT scanning in 48 of the 54 patients detected 61% of the lesions present and angiography in 35 patients detected 52% of the lesions present. In a segment by segment analysis, ultrasonography detected more lesions in the left lobe than CT scanning. CT scanning failed to detect 70% of the metastases present in segments 2 and 3 whilst ultrasonography failed in 23%. Ultrasonography also had a greater sensitivity for metastases of less than 2 cm in diameter. The results of ultrasonography and CT scanning, in this series were complimentary and had a combined accuracy of 81% for the right lobe and 76% in the left. Other studies however, have failed to show a significant advantage to CT scanning over USS (Smith TJ, 1982)

II.F.3.a. Enhancement of preoperative ultrasonography

Attempts have been made to improve the sensitivity, specificity and accuracy of preoperative ultrasonography by altering the relative acoustic impedance of the tumour deposits to the surrounding liver. Injection of microbubbles of carbon dioxide into the hepatic arterial circulation has been used to produce this effect (Matsuda Y, 1986). Forty three patients with histological confirmation of hepatic malignancy underwent enhanced ultrasonography. Carbon dioxide microbubbles were introduced via an angiogram catheter into the coeliac, common hepatic or superior mesenteric artery. Different effects were seen with different pathologies and different patients. The effects noted were hyper-echoic change, iso-echoic change, hypo-echoic change with a hyper-echoic rim, marginal spotty hyper-echoic change and internal spotty hyper-echoic change. Hepatocellular carcinomas predominantly showed hyper-echoic change while metastatic tumours tended to show hypo-echoic

change with a rim sign. Contrast enhancement lasted for between 3.5 and 4 minutes. Enhancement improved the detection of small (less than 2 cm) hepatocellular carcinomas by 19 % and also allowed some differentiation of the nature of the tumour by its pattern of enhancement.

II.F.4. Computerised axial tomography in the preoperative assessment of hepatic metastases

There are few papers describing the use of CT scanning in the preoperative staging of the liver in patients with colorectal cancer. In clinical practice the use of this investigation has been limited by cost, a lack of perceived benefit and availability. Finlay (1982) showed that CT scanning of patients following curative resection for colorectal cancer would detect hepatic metastases which were otherwise occult. of 35 patients having curative resection of primary colorectal cancer, immediate post-operative CT scanning detected occult metastases in 11, these metastases being confirmed on subsequent sequential CT scanning. Follow-up showed a 30 month survival of 9% for those with metastases compared to 88% for those without. Smith (1982) prospectivly compared both unenhanced and water-soluble contrast (Iotholamate Meglumine Injection USP 60%) enhanced CT (EMI 5005 or General Electric 8800 body scanner) scans to preoperative ultrasonographic examination and hepatic scintigraphy in 80 patients. Forty seven of the patients had normal livers on palpation and visualisation at surgery. Smith found that CT scanning detected only 12 of 49 lesions, 2 cm or smaller in diameter, that had been detected by surgical exploration. It is likely that a number of smaller lesions were missed by both techniques (Ozarda A, 1962)

II.G. Iodised oil emulsion enhancement of CT scans

II.G.1. Introduction

Routine CT scans are enhanced by the injection of a water soluble contrast agent prior to and during the scan sequence, this is called dynamic bolus enhancement (DBCT). The contrast injected prior to the scan is distributed throughout the extra cellular component of the total body water. The contrast injected during the scan remains in the circulation while the images are being obtained.

Iodised oil emulsion (IOE) enhancement of CT scans is a technique that has been developed in Edinburgh (Miller AM, 1990) which improves the detection of primary and metastatic malignancy in the liver by increasing the radio density of normal liver without effecting that of tumour deposits. A similar technique has been reported in the American literature using an agent called EOE-13 (Grimes G, 1979; Reed WP, 1986; Miller DL, 1984; Lewis E, 1982; Ward BA, 1989). The technique involves the peripheral infusion of an iodinated oil as a stable emulsion in a measured dose.

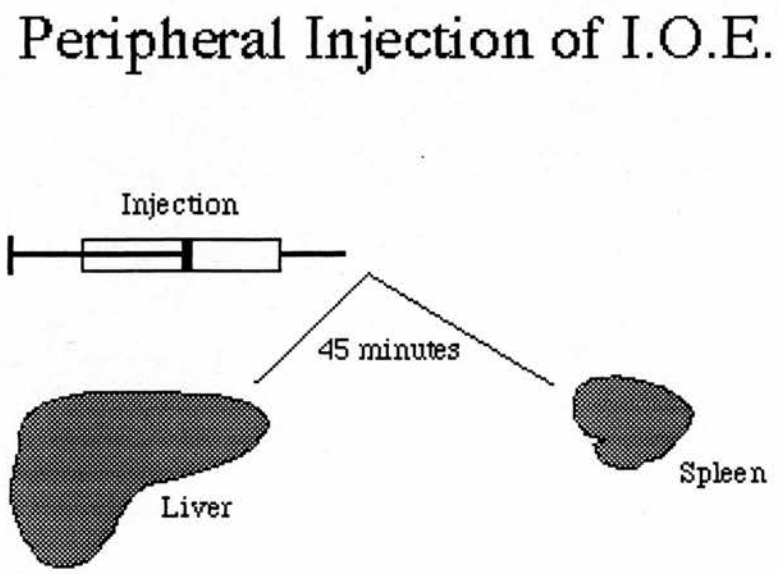

Fig 8. The peripheral injection of IOE (over a period of 45 minutes) is taken up by the liver and spleen after a further 45 minutes. Patients are premedicated with 100mg of hydrocortisone to prevent reactions to the IOE.

The particle size of the emulsion is controlled at preparation to remain between 2 to 4 μm. These particles are able to pass from the venous

circulation to arterial circulation without becoming entrapped in the pulmonary or splanchnic capillary beds. The oil micro droplets are removed from the circulation by cells of the reticuloendothelial system within the liver and spleen (*Fig 8.*).

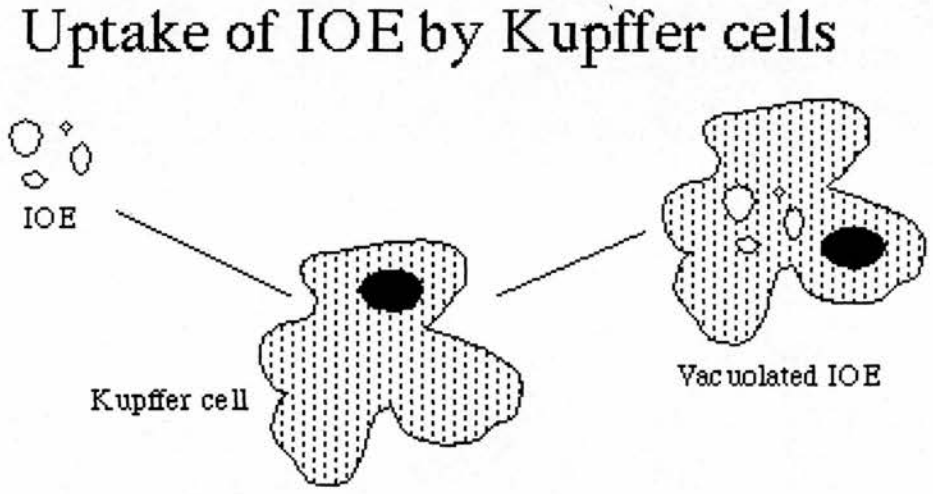

Fig 9. Uptake of the IOE by the Kupffer cells and its vacuolisation within the cells.

In the liver, Kupffer cells fill with the iodinated oil (*Fig 9.*) and become radio dense. This causes an increase in radio density of all areas of normal parenchyma within the liver.

Areas of abnormal liver, not containing functioning Kupffer cells have no increase in density. On subsequent CT scanning, normal areas of the liver and spleen have a high radio density and so higher attenuation of the X-ray signal. Areas that do not contain active Kupffer cells (such as tumours) show no change in density (*Fig 10.*).

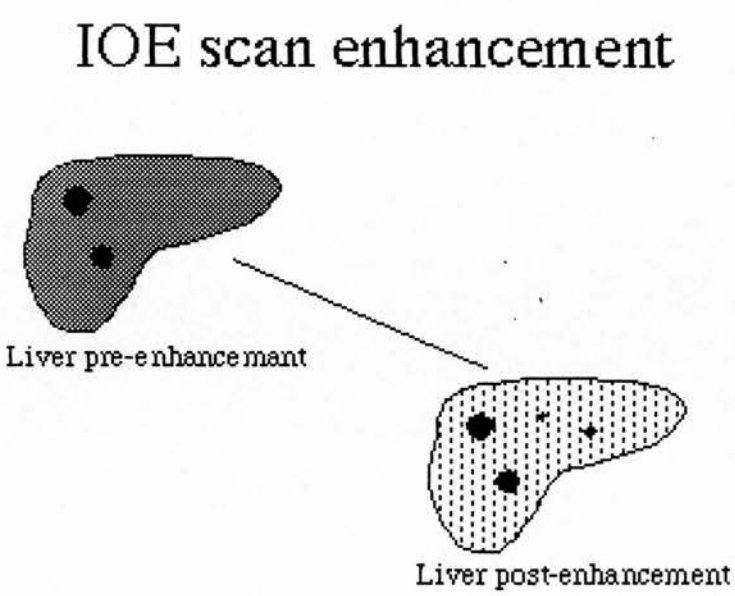

Fig 10 Post IOE injection enhancement of the liver scan

Infusion of emulsions of iodinated oil have been shown to increase the radio density of both the liver and spleen on plain radiography, but the dose required to cause sufficient enhancement of a plain radiograph was found to be too toxic. Subsequent development of the technique using a lower dose and CT scanning instead of plain radiography showed improved delineation of tumour and reduced side effects (Grimes G, 1979). The more recent publications using EOE-13 advocated the use of a pre-infusion injection of hydrocortisone to reduce the unwanted side effects. This does not affect the quality of image-enhancement (Ward BA, 1989). EOE-13 enhanced CT scanning in this study was as sensitive and more accurate than either arterial portography or nuclear magnetic resonance imaging. Because of the initial problems of toxicity, EOE-13 has not found favour as method of investigation in the United States of America where it was initially developed. The Department of Radiology of the University of Edinburgh has continued research and development of this technique as IOE scanning. The technique is now a fully established service in the Department of Radiology of the RIE and the Hepato-Biliary unit of the RIE.

II.G.2. Conclusion

There are two principle factors that will continue to confound the accuracy of pre-operative hepatic ultrasonography. Firstly, as demonstrated by McGarrity (1987), the anatomical site of the tumour may preclude its detection: significantly fewer small tumours are detected in the posterior part of the right lobe than in the rest of the liver. This finding is supported by Clarke (1989). The morphology of the patient may also have considerable relevance as thick layers of subcutaneous fat and muscle may reduce the quality of a preoperative ultrasonographic scan (McDicken WN, 1991).

These factors can be overcome at operation by placing the ultrasound probe in direct contact with the liver. Signal attenuation caused by interposed tissue is eliminated and access to the posterior portion of the right lobe and the whole of the left lobe of the liver is improved. By its very nature, IOUSS includes palpation of the liver and this contributes to the detection of small subcapsular lesions. These major advantages, plus the ability to biopsy any lesion that may be identified, have led to an increase in the use of intraoperative ultrasonography at the time of operation for known hepatic metastases.

Intraoperative ultrasonography represents the gold standard for the imaging of known hepatic malignancies and has been used in a large scale trial of hepatic evaluation in patients undergoing curative resection of colorectal cancers (Machi J, 1991). There are a number of potential benefits to IOUSS: immediate accurate hepatic imaging, targeted biopsy of any suspicious lesions seen and very low cost.

II.H. Aim

This thesis will evaluate the use IOUSS and IOE scanning in the detection of occult hepatic metastases in patients undergoing curative resection for colorectal cancer.

To confirm that IOE scanning is superior to DBCT in the detection and definition of hepatic tumour, both of these investigations have been performed on a group of patients known to have hepatic malignancy. The results of these investigations have been compared with regard to the volume of liver involved and the accuracy of the investigation in determining if the tumour was resectable or not. The results of the preoperative investigations have been compared to the operative findings including intraoperative ultrasonography.

To show that IOUSS can detect all occult hepatic metastases, IOUSS has been compared to IOE scanning at the time of operation and to IOE scanning at 6 monthly intervals for 4 consecutive scans. This will confirm that IOUSS is the investigation of choice for the detection of occult hepatic metastases at the time of surgery for colorectal cancer.

Furthermore, to show that the presence of occult hepatic metastases has a powerful effect on outcome, the survival of patients with and without hepatic metastases is calculated and compared.

The superior staging and follow-up of patients in these series will be used to further clarify the relationship of CEA to the presence of hepatic metatases both at presentation and during follow-up.

Finally, this thesis will show that the information obtained by the use of intraoperative ultrasonography may be used to successfully select patients with hepatic metastaes for hepatic resection.

Chapter III

Methods of imaging investigations

III.A. Technical description of methods

III.A.1. Introduction

A number of investigative techniques have been used in the evaluation of patients involved in the studies that comprise this thesis. The method of each investigation is described here and referred to in subsequent chapters. The method of laparoscopic ultrasonography and of data storage and analysis form separate chapters.

III.A.2. Investigations undertaken

The following investigative techniques were used to evaluate patients: chest radiography (X-ray), abdominal ultrasonography (USS), thoracic and abdominal computed axial tomography scanning with water soluble contrast enhancement (DBCT), selective and highly selective angiography, iodised oil emulsion enhanced CT scanning (IOE), intraoperative and laparoscopic intraoperative ultrasonography and biopsy (IOUSS).

III.A.2.a. Chest radiograph.

All chest X-ray films (a single view postero-anterior film) were taken in the main X-ray department of the Royal Infirmary of Edinburgh (RIE) or in the X-ray department of the Eastern General Hospital (EGH). All of the films were viewed and reported by a consultant radiologist.

III.A.2.b. Ultrasonography

In the evaluation of patients with known metastases, ultrasonography was undertaken as part of the pre-operative staging and was performed by one of the radiologists of the RIE Department of Radiology. The reports were checked by a consultant member of staff and experienced hepatic ultrasonographer. All scans were performed using a 3.5 MHz sectoral scanning probe (Acuson).

A standard investigation was performed with the patient in the supine position following a 6 hour fast. Contact gel was used to improve ultrasonic coupling and the images were stored on photographic film. Patients were also scanned sitting up and in the left lateral position to improve the visualisation of the postero-superior portion of the right lobe of the liver (segments VII and VIII).

III.A.2.c. Thoracic CT scanning

All thoracic and abdominal CT scans were performed at the RIE. The patients were fasted prior to the CT scan which was performed without contrast enhancement. The scans were obtained in 10 mm slices at 10 mm intervals with breath holding. Dynamic interpretation was undertaken and the images transferred to photographic plates for storage.

III.A.2.d. Abdominal CT scanning

All abdominal DBCT scans in the series were obtained with dynamic bolus contrast enhancement. Intravenous access was obtained via a butterfly needle in the dorsum of the hand or by intravenous canula. The scans were undertaken in three phases.

Scout views

A longitudinal antero posterior image of the patient to map the level of the most superior and the most inferior parts of the liver was obtained. In patients with known or suspected pelvic tumour the scout view included the pelvis.

Plain scans

A scan sequence was obtained with slice thickness of 15 mm and a slice interval of 15 mm without contrast enhancement in patients who had a contraindication to iodine-based contrast agents. Unenhanced scans were also performed in patients who had a lesion suspected of being a haemangioma.

Dynamic bolus enhancement

Prior to commencement of each run, a single intravenous injection of 50 ml Niopam 300 (E. Merck Pharmaceuticals) was given via an indwelling canula. A further 50 ml of Niopam 300 was infused during the first half of the scan sequence giving a total dose of 100 ml (30 grams of Iodine). Patients with gastric, pancreatic or biliary lesions were given an oral meal of dilute barium immediately prior to scanning. The scans were undertaken with a slice thickness of 10 mm and a slice interval of 10 mm. Ten to 12 images were obtained depending on the size of the liver. The patients were asked to hold

their breath during the acquisition of each image. Following each run the images were viewed to ensure the technical adequacy of the scan. Magnified images were obtained of areas of interest. If the scans were not of satisfactory quality the run was repeated on a separate occasion (*Plate 1.*).

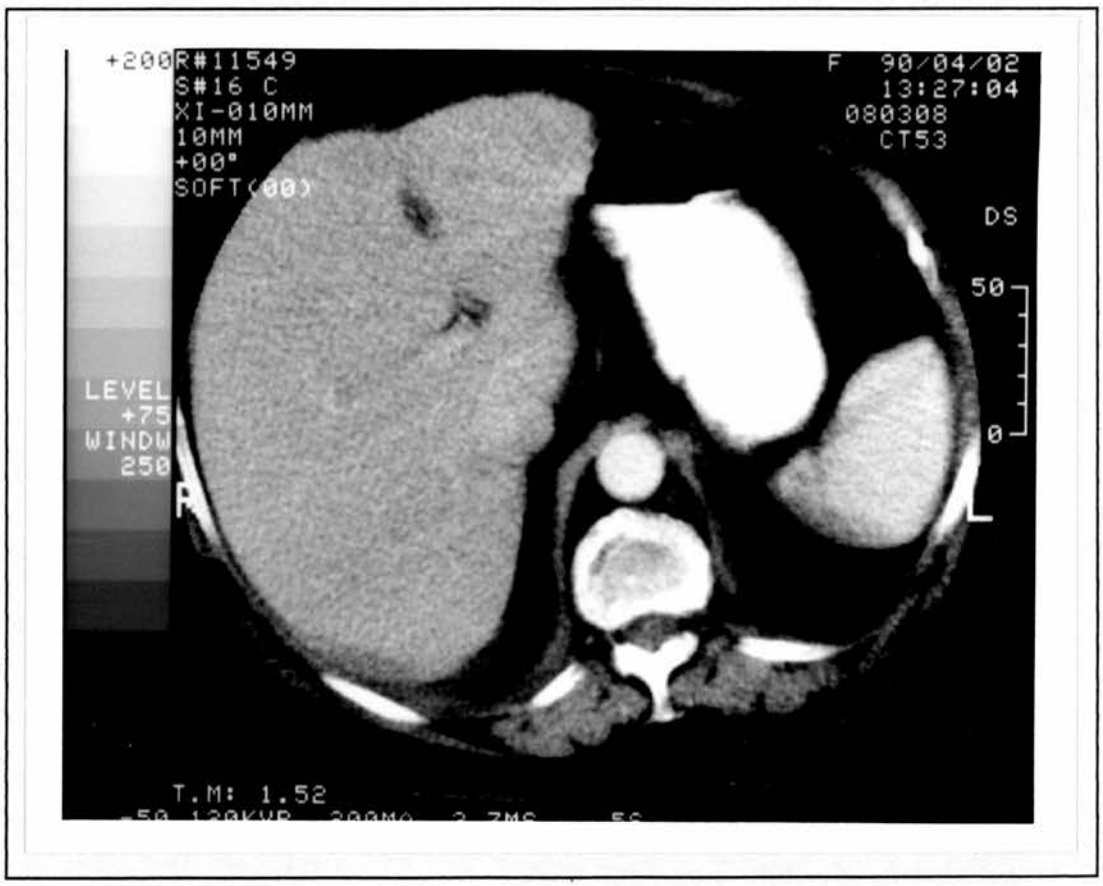

Plate 1. DBCT scan of the right lobe of the liver in a patient wtih suspected hepatic metastases from a colorectal cancer.

III.B. Iodised oil emulsion enhanced CT scanning

III.B.1. Preparation of iodised oil emulsion

The iodised Oil Emulsion was prepared in a standard manner. Using a 2K Standard Short Sealed Unit Laboratory Mixer (Silveron Machines), the detachable head and emulsifier screen are sterilised by autoclaving. All glassware is sterilised by hot air and all instruments and glassware are rinsed in Sterile Water for Injection BP or particle-free ethanol, prior to use. A mixture of 25g of Soya lecithin (INC. Biochemical) and 100 ml of Dehydrated Alcohol

BP are stirred for 20 minutes. The ethanolic extract of lecithin is then obtained by vacuum filtration of the liquid phase through a 5 μm PTFE filter (Mitex, Millipore). All further preparation is undertaken in a laminar flow cabinet under aseptic conditions. Iodised Oil Fluid Injection BP (Lipidol Ultra Fluid, May and Baker) 200 ml is placed in a 500 ml conical flask. The ethanolic extract of lecithin, 50 ml is filtered through a 220nm millex FG filter (Millipore) and placed into the flask, covered and placed in a water bath at 60 degrees centigrade along with a similar, covered, 500 ml flask containing Water For Injection BP 250ml. The water for injection is then transferred to a 500ml beaker and placed beneath the homogeniser. With the homogeniser running at full speed the lecithin/iodised oil mixture is added in 50 ml aliquots, with two minutes of homogenisation between each addition. The final preparation is then aliquoted into 10 ml rubber capped multi-dose vials for subsequent use.

Using this technique, a stable emulsion is created with a mean particle diameter of 3 μm. The emulsion is stable over time with no appreciable change in the distribution of particle size over a three month period. The emulsion is also stable on dilution to more than five times its original volume with Glucose Intravenous Infusion 5% BP.

III.B.1.a. Administration

The dose is calculated at 0.2 ml of the emulsion per kg body weight and diluted to 45 ml total volume with 0.5% dextrose infusion BP on the morning of the scan. This diluted mixture is then infused into a peripheral vein over a period of 45-60 minutes. Prior to the infusion the patients are given a single dose of hydrocortisone 100 mg BP. The patients, vital signs are monitored at 15 minute intervals during the infusion and at half hourly intervals thereafter for a further three hours. A delay of 40 to 60 minutes is allowed between the end of the infusion and the start of the scan to allow all of the emulsion to be removed from the circulation by the reticuloendothelial system.

III.B.1.b. Scanning

Following the infusion of the IOE, patients are transferred to the CT scanner. Scout views are obtained to identify the level of the superior surface of the liver and its most inferior point. Serial scans are then taken at 10mm intervals with

a slice thickness of 10 mm. The patients are required to breath hold for the image acquisition time of the scanner (8 seconds). Following the acquisition the images are reviewed and any areas of interest interrogated further. Final evaulation is made from the X-ray plates of the scan, the images being stored as hard copy and on laser disc. The patients return to the ward following the scan and are monitored for a further 3 hours by recording their pulse, blood pressure and temperature at 30 minute intervals.

III.B.1.c. Reporting

The IOE scans were reported by one of two consultant radiologists (LT, PA), blind to the results of other investigations. Each image of the scanning sequence was dynamically interrogated to produce the maximum differentiation between the enhanced liver parenchyma and the unenhanced tumour deposits.

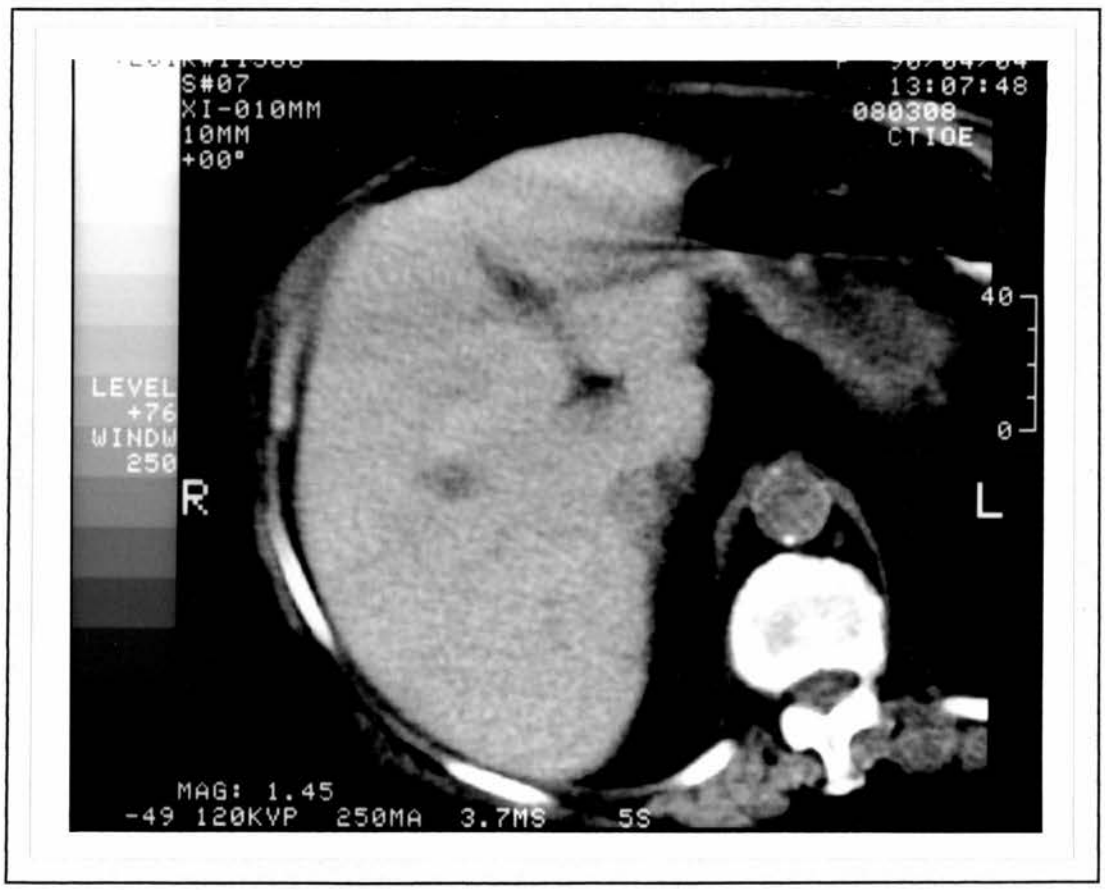

Plate 2. IOE scan of the same patient as plate 1 revealing a small (1.4 cm) metastasis lying between segments V and VIII.

The hepatic vascular anatomy was identified by the continuation of vessels from one image to another though the sequence of the scans. Metastases were identified as areas of low attenuation not corresponding to a vessel (Plate 2.).

The site of each metastases was recorded using hepatic segmental anatomy (Bismuth H, 1982) (Plate 3.) .

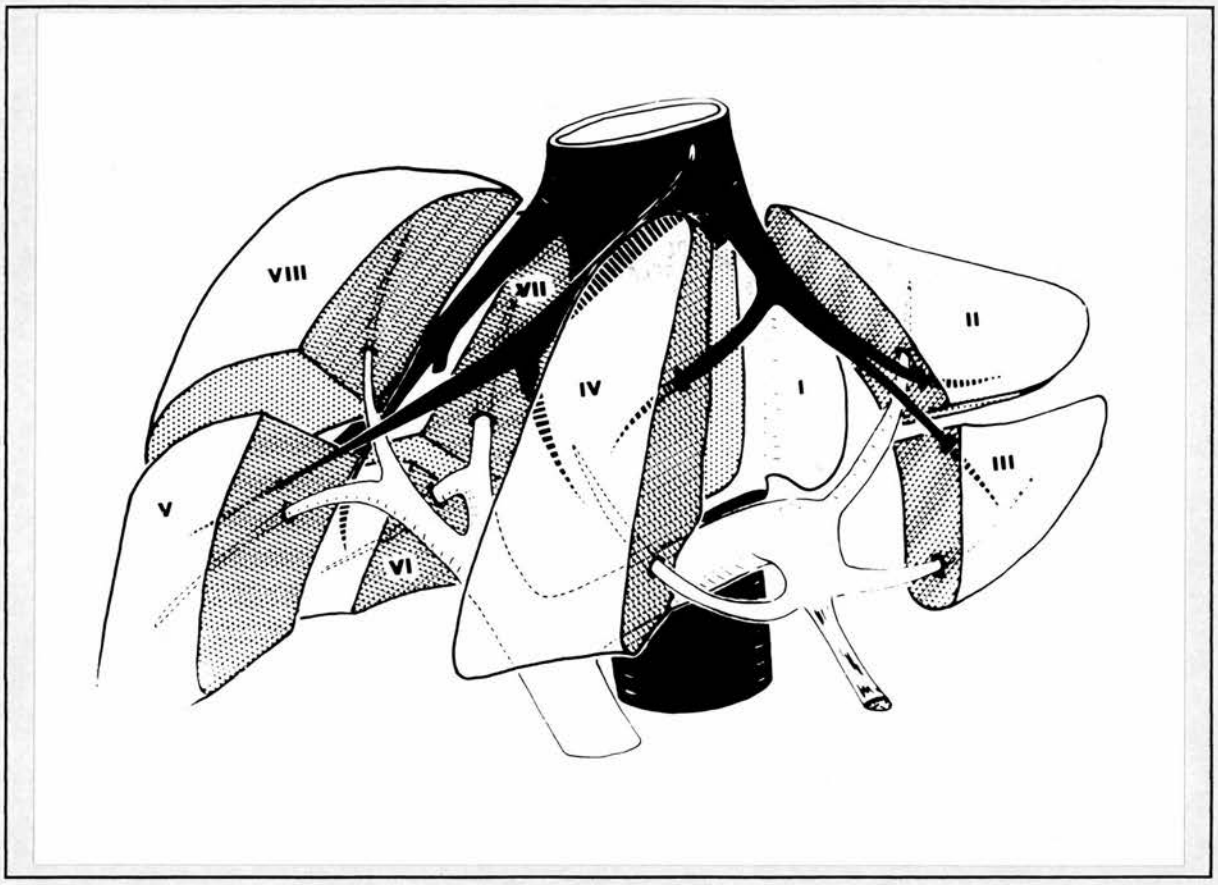

Plate 3. The segmental anatomy of the liver after Castaing, the segments are separated by the intra-heptic branches of the hepatic veins (black) and supplied by the branches of the portal vein (white). There are eight segments, four on the left and four on the right.

III.B.2. Appearances of lesions on IOE scanning

A number of normal and abnormal appearances were seen on IOE scanning, not all of which could be easily differentiated from tumour or metastases. The overall increase in attenuation of the liver parenchyma was directly related to the ability of the reticuloendothelial system to successfully remove the emulsion from the circulation.

III.B.2.a. · Normal liver.

Scan images are identical in format to a standard DBCT scan in that the sequential scans are recorded as digital images on a computer disc and recalled as required. Normal liver appears as an amorphous grey of similar attenuation to the spleen and of higher attenuation than the kidneys or pancreas

Major intrahepatic vessels appear in cross or tangential section and are seen as either circles or ellipses of low attenuation; this is in contrast to DBCT where they are of higher attenuation. Vessels are recognised by their anatomical site and by their appearance on more than one slice at a site contiguous with areas of similar attenuation and position on the previous and subsequent slices of the series. The gallbladder is identified by its position and the presence within the lumen of low attenuation bile and, in some cases, gallstones. The intrahepatic portion of the inferior vena cava is also identified by its low attenuation and its anatomical position. Bile canniliculae, intrahepatic radicals of the biliary tree and the right and left hepatic ducts are not normally seen on IOE images of the liver. The intrahepatic radicals of the hepatic artery are not seen by IOE scanning.

III.B.2.b. Benign lesions seen on IOE scanning.

Any area of the liver parenchyma that has a reduced number of Kupffer cells in it will appear as an area of reduced attenuation on IOE scanning. Reduced attenuation will also occur in areas of the liver that have a relatively reduced blood supply from either the hepatic arterial or portal venous circulation.

III.B.2.c. Benign liver cysts

Liver cysts are the most common benign abnormal finding on IOE scanning and appear as areas of very low attenuation with smooth outline and near spherical form. Cysts were also the most common benign lesion to be confused with tumours on IOE scan images.

III.B.2.d. Haemangiomas

Small haemangiomas may also be detected by IOE scanning and mimic small metastases or malignant tumours. Differentiation of these two findings is not possible from a single IOE scan. However haemangiomas may be recognised by their increase in attenuation on administration of water-soluble contrast during a DBCT scan and so, in this regard, the information from these two

investigations is complementary.

III.B.2.e. Fibronodular hyperplasia

Areas of fibro nodular hyperplasia within a normal liver may have exactly the same appearance as a tumour or a metastasis on IOE scan. It is impossible to differentiate between these lesions and tumour by IOE scan.

III.B.2.f. Malignant lesions on IOE scanning

A lesion seen on IOE scanning may have a number of features that suggest malignancy. Highly suspicious features are;

- Low attenuation and irregular outline in a larger lesion.

- A lesion of mixed attenuation.

- A small area of low attenuation which does not correspond to the expected site of a vessel and is not present on sequential images of a run.

- An area of low attenuation surrounded by one or more smaller satellite areas of low attenuation.

- An area of low attenuation associated with a segmental perfusion defect: this is suggestive of carcinoma with involvement of the portal vein and hepatic arterial supply causing an area of non-functioning liver.

- A centrally placed area of low attenuation with evidence of peripheral intrahepatic biliary dilation.

- Peripherally placed areas of low attenuation which demonstrate invasion into adjacent anatomical structures.

III.B.2.g. Hepatocellular carcinomas

The appearance of hepatocellular carcinomas is essentially the same as on DBCT scanning. The increase in the difference in attenuation between normal liver and tumour afforded by IOE scanning reveals more of the small daughter nodules which may be present (Plate 4 and 5). IOE scanning does not improve the detection of intra-vascular spread of tumour.

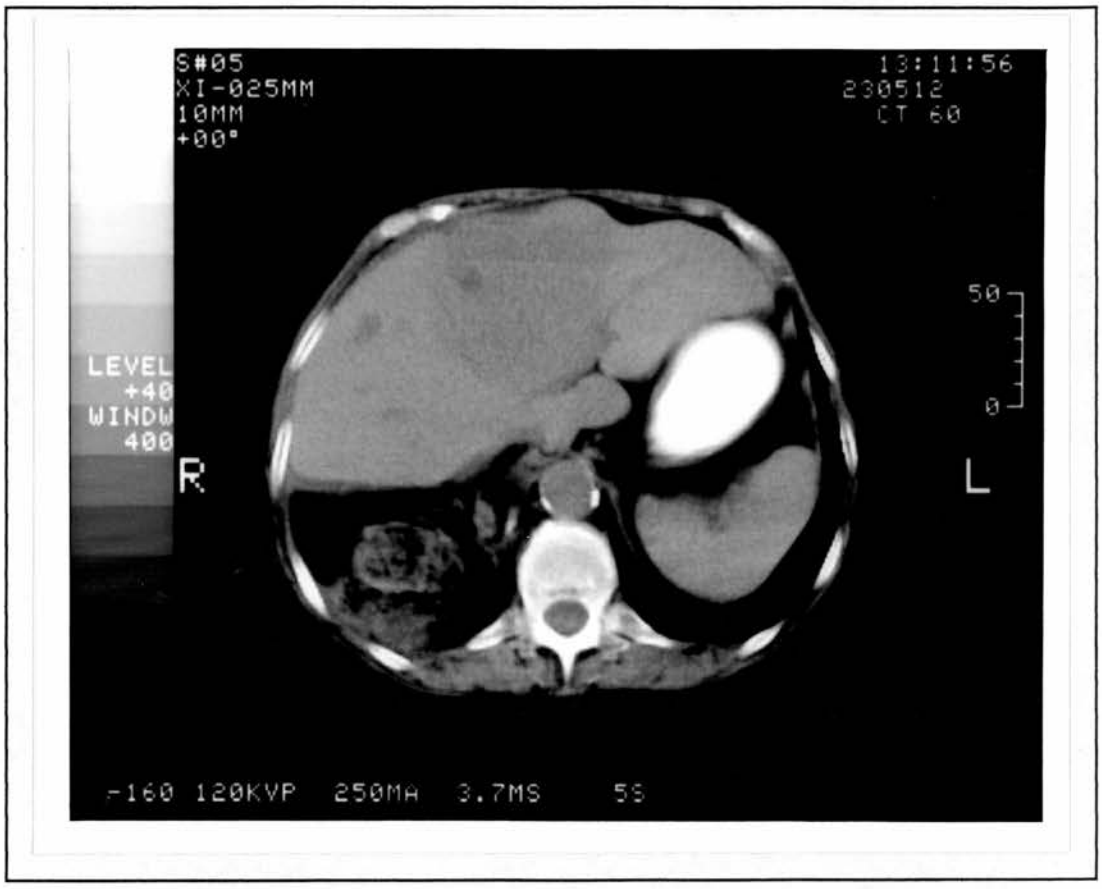

Plate 4. DBCT of a hepatocellular carcinoma of the liver occupying segment IV with daughter nodules in segments V and VI.

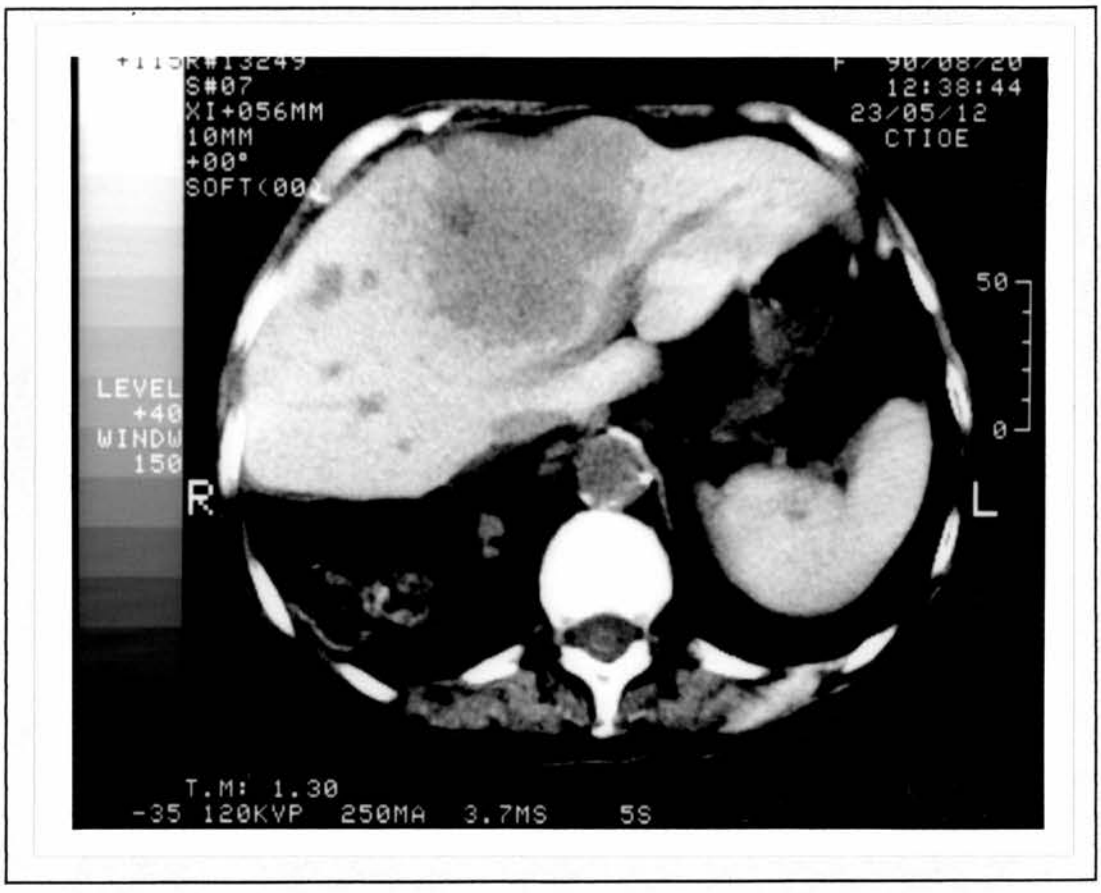

Plate 5. IOE scan of the same lesion showing increased attenuation of the normal liver more clearly revealing the daughter nodules in the right lobe.

III.B.2.h. Cholangiocarcinomas.

Whilst intra-hepatic cholangiocarcinomas are rare, the effects of extra-hepatic lesions may be seen. Metastases from cholangiocarcinomas are also uncommon; when present they appear as low attenuation lesions on the IOE scan.

III.B.2.i. Metastases from colorectal cancers.

Metastases from colorectal cancers may present with a number of features. They vary in size from so small as to be undetectable to single lesions occupying an entire lobe of the liver. They are generally more radio dense than unenhanced blood vessels and less dense than the enhanced liver. They may have a smooth outline and be of regular shape or they may be irregular and spiculated. Large lesions may be of irregular density and, if necrotic in the centre, may be of particularly low attenuation. Colorectal metastases which

have originated by transcoelomic spread may form subcapsular lesions which, if small, are difficult to detect because of the adjacent structures. Metastases from mucinous tumours may form complex cysts, the internal septa of which are apparent on both IOE scanning and on DBCT. The appearances of metastases on IOE and DBCT scanning are essentially similar but the contrast between metastases and normal liver is increased by IOE enhancement (Plates 6,7,8,9).

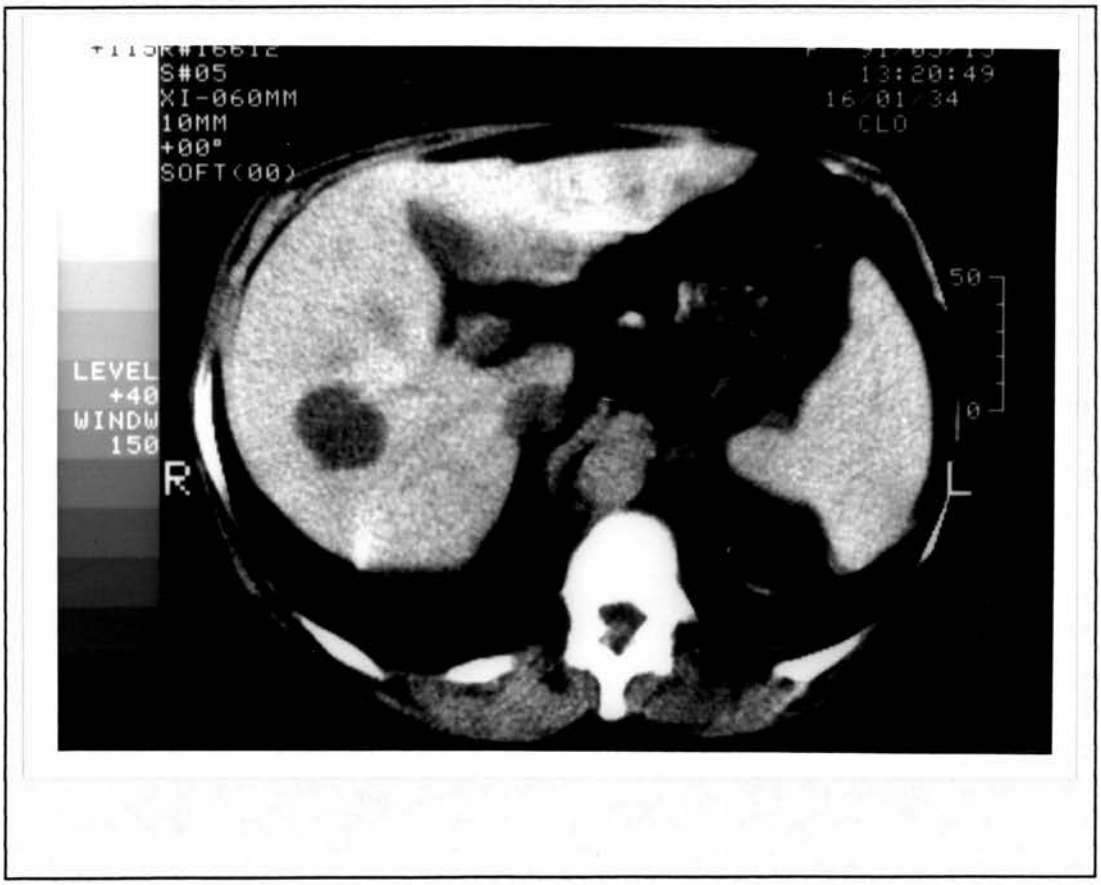

Plate 6. DBCT of a malignant hepaic cyst from a mucinous adenocarcinoma of the colon.

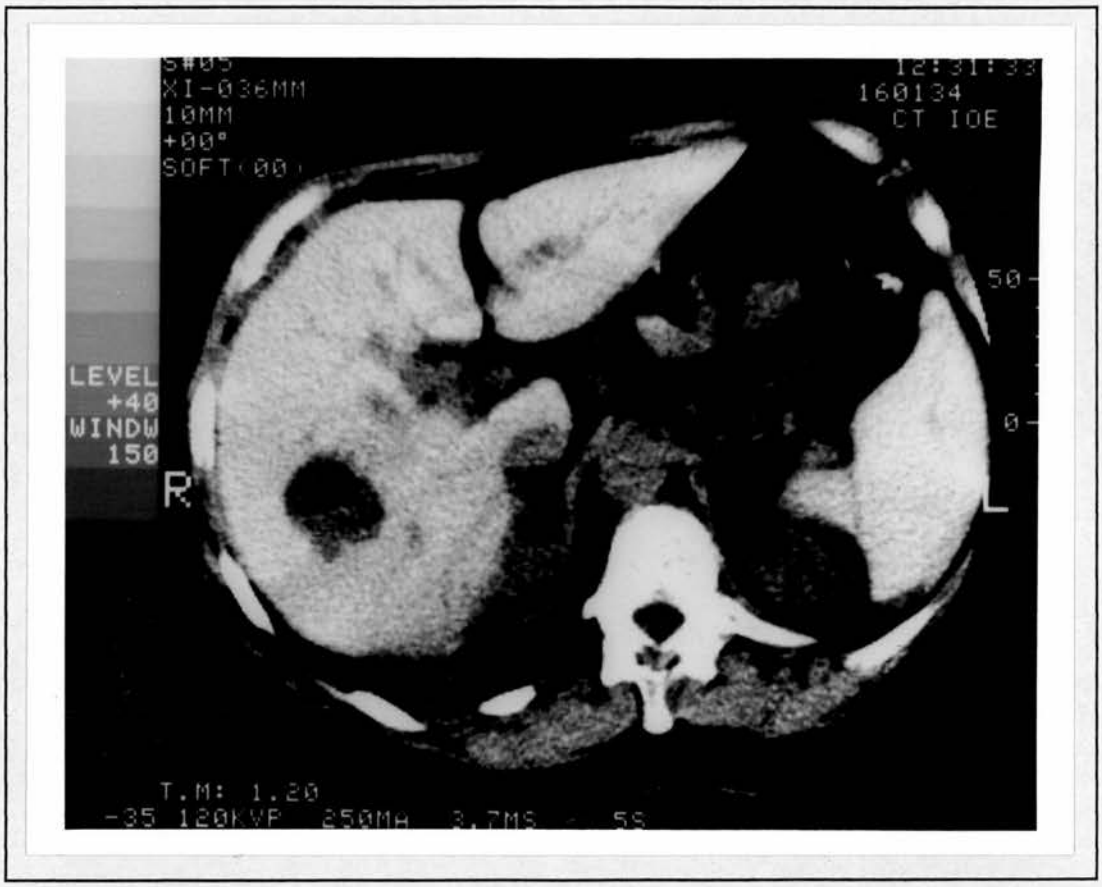

Plate 7. IOE scan of the same patients showing increased definition of the cyst and the presence of internal septa.

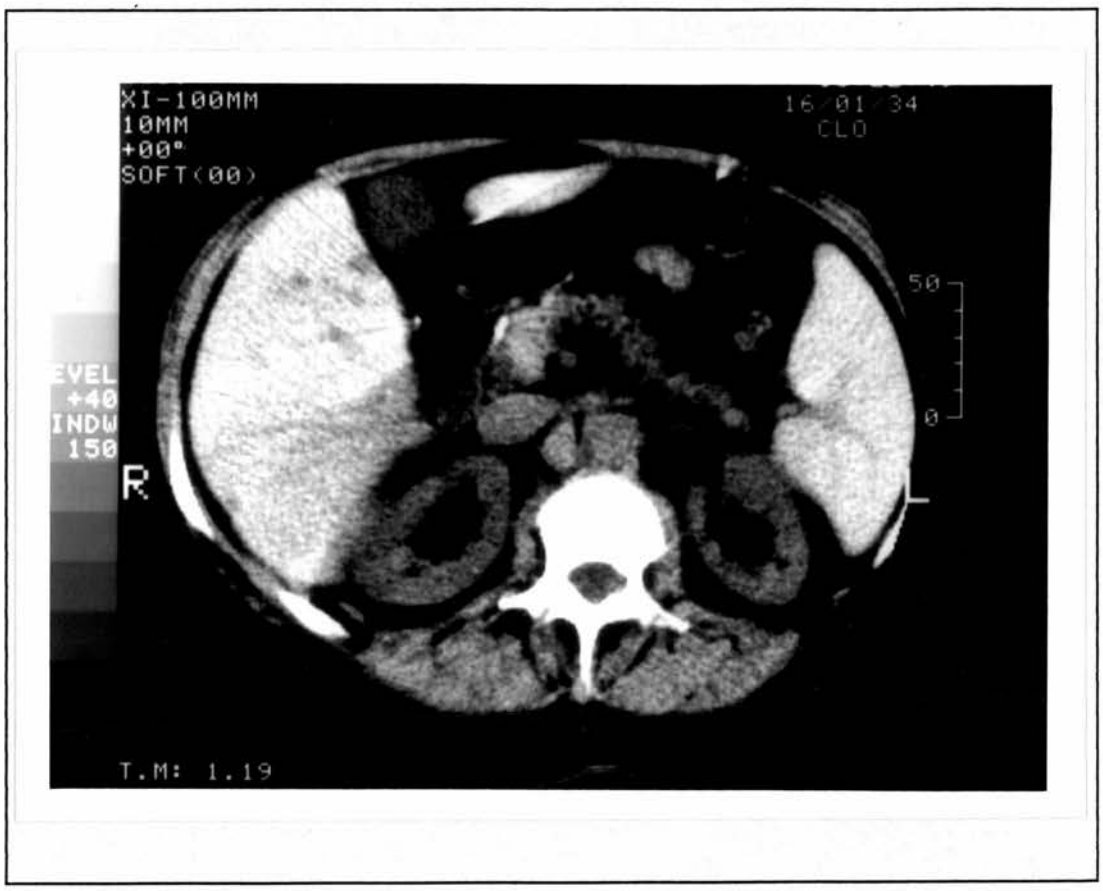

Plate 8. DBCT of segments V and VI in the same patient.

Plate 9. IOE scan of segments V and VI in the same patient revealing a further small malignant cyst not seen on DBCT scanning.

There are no special features of colorectal metastases which allow confident diagnosis of the primary from the IOE appearances of the hepatic metastases alone. It is not possible to determine the site of a primary cancer by the IOE appearance of the metastases in patients who have occult primary disease.

III.B.2.j. Recording

Each lesion was recorded by its site and its size. The site is described with reference to the segmental liver anatomy described by Bismuth. Size was measured as the maximum recordable diameter on the scan image. In the series of patients being assessed for resection of liver tumours, the scans have been reported in terms of the maximum number of hepatic segments involved rather then just the number of metastases present, as this gave a better representation of the anatomical resectability of tumours as well as the number of metastases involved.

III.C. Intra-operative Ultrasonography

III.C.1. Introduction

Intra-operative ultrasonography was performed by placing a sterilised linear array 5 MHz "T" shaped ultrasound probe directly onto the surface of the liver. Direct access to the surface of the liver increased the volume of liver which could be visualised compared to pre-operative ultrasonography. The reduction in attenuation of the ultrasound beam allowed the use of a 5 MHz probe as opposed to the 3.5 MHz probe thus giving improved definition. Increased definition allied to the improved access to the liver afforded by laparotomy allowed the interrogation of structures within the liver from a number of different viewpoints with great clarity.

III.C.1.a. Equipment

The Aloka SSD 210 II with a 5Mhz 'T' shaped ultrasound probe was used for the investigations except for a short period of time when due to failure of the 'T' probe a finger shaped probe was used (Plate 10). A 7.5 MHz endo-anal probe was used for the laparoscopic ultrasonography .

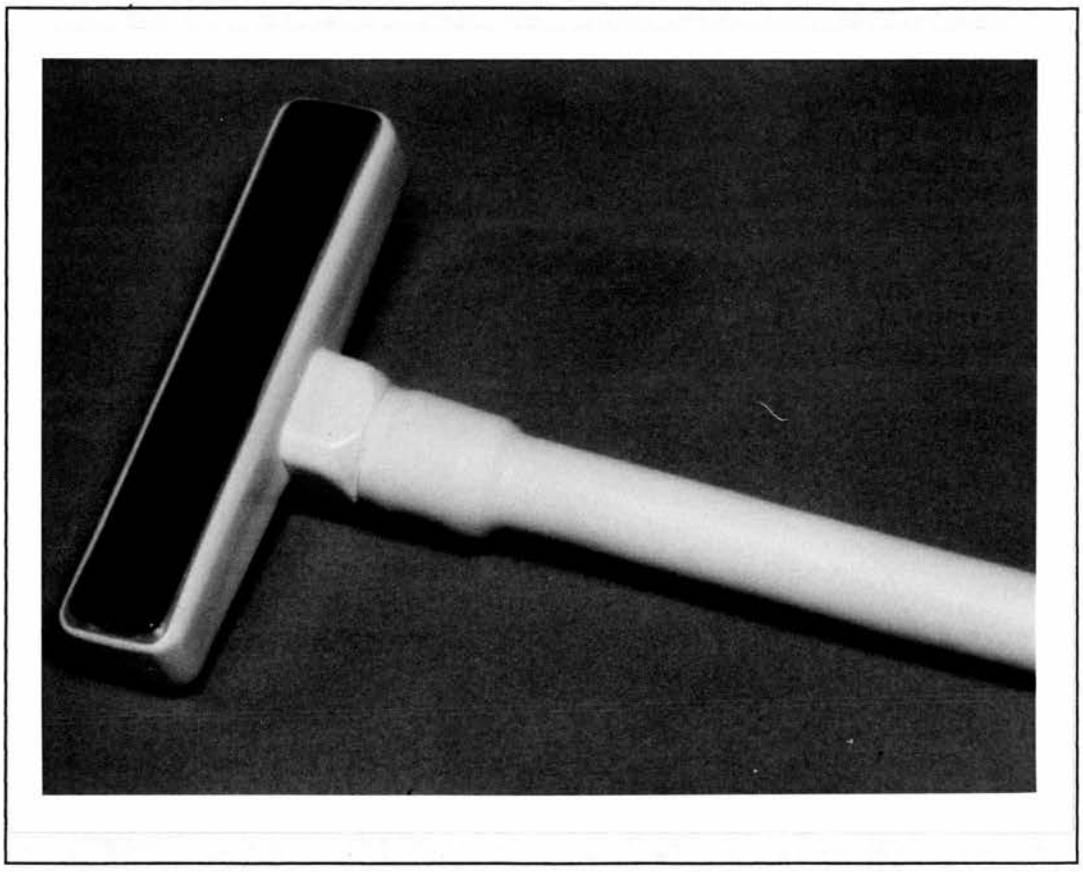

Plate 10. Aloka 5 Mhz "T" probe used for the intraoperative hepatic scanning of patients undergoing curative resection of colorectal cancers.

III.C.1.b. Technical details

The Aloka SSD 210 II is a portable ultrasound camera capable of supporting a number of compatible ultrasound probes. Scanning is by electronic linear scanning with 40 piezoelectric crystals in the scanning head. The scan obtained has a width of 56 mm and a depth of 147 mm. This machine has a maximum frame rate of 30 frames /second. The fixed focus is obtained by transmission /reception electronic focusing plus an acoustic lens. Time biased gain is variable: near field -80 to -10 dB, far field 0 to +5dB. The final image is displayed on a 13.75 cm video screen and may be transferred to a video printer for permanent record.

III.C.1.c. Method

Prior to laparotomy, the ultrasound probe (Aloka UST-5810T-5) is sterilised by immersion for 15 minutes in gluteraldehyde solution (Cydex). Only the

scanning head and cable are immersed as the multipoint connector to the Echo-camera is not waterproof. Following Cydex immersion and in the sterile field, the cable and head are rinsed by immersion in 1L of Sterile Water BP for 1 minute and then dried. The multi connector is held out of the sterile field and connected to the Echo-camera and the cable fixed to the operating drapes to prevent it from contaminating the operating field. Following standard skin preparation and draping, laparotomy is performed usually via a bilateral subcostal incision in patients for hepatic resection and either a midline, paramedian, or lower transverse incision for colonic resections. Bimanual palpation of the liver is then undertaken. In patients who were being assessed for resection of hepatic tumour, the liver is mobilised by division of the falciform ligament and the triangular ligaments to allow complete examination of the surface segments II, VII and VIII. Firstly, light palpation is undertaken to examine the surface of the liver for studding by transcoelomic metastases. Deep palpation is then undertaken with one hand on the upper surface of the lobe and one beneath. Firm pressure is applied between the fingertips and with a rubbing motion the substance of the liver examined. Large metastases within the substance of the liver are detected in this manner and their approximate site noted.

In patients having primary resection of colorectal cancer any non anatomical adhesions to the liver are divided but no other mobilisation of the liver is undertaken. Particular attention is paid to light palpation of the surface of the liver to detect subcapsular metastases in these patients because of the near field loss of image. A stand off was not used in these patients as it was found to be impractical to perform the examination in this way. Following palpation the liver is systematically examined using the ultrasound probe (Plate 11).

Plate 11. A 5Mhz probe on the surface of the liver.

The examination is guided by the intra-hepatic vascular anatomy and by this means the entire internal volume of the liver can be visualised. All of the initial scanning was undertaken with the probe head in a sagittal plane with the scanning array in contact with the anterior surface of the liver and directed posteriorly.

III.C.1.d. Identification of the major vascular structures.

With the probe on the surface of segment IV, the inferior vena cava is identified and followed superiorily to the level of its junction with the hepatic veins. Further superior movement of the probe is prevented by the right triangular ligament (*Fig 1, Plate 12*).

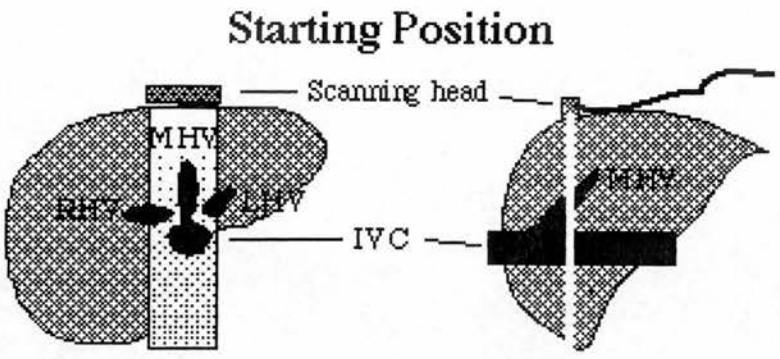

Fig 1 initial position of scanning head to identify the major intra-hepatic vessels, RHV- Right Hepatic Vein , MHV- Middle Hepatic Vein, LHV-Left Hepatic Vein, IVC - Inferior Vena Cava. The 5 MHz probe is placed on the anterior surface of the liver and angled posteriorly .

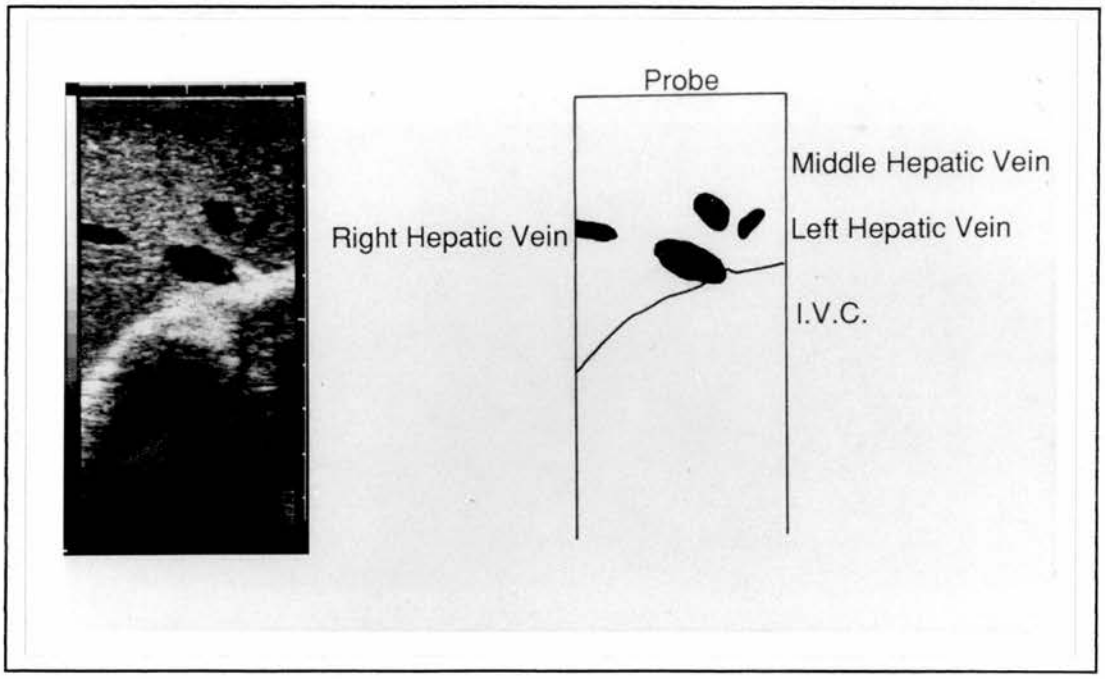

Plate 12. Position 1 showing the right, middle and left hepaic veins and the inferior vena cava.

To visualise the most superior part of the liver, the plane of the probe head is angled superiorily until the inferior aspect of the heart comes into view. From this point (*Fig 2 the most superior aspect of segment IV*) the probe is angled inferiorly until the plane of scan is vertical.

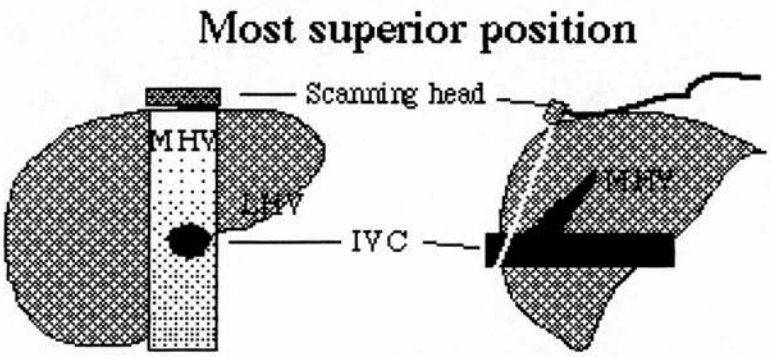

Fig 2 Most superior position of scanning head. If the scanning head is angled superiorily following the IVC , the lower portion of the right atrium and right ventricle come into the plane of the scan.

The probe is then moved inferiorly across the surface of the liver imaging the volume of liver anterior to the inferior vena cava. As the probe is drawn across the liver the angle of the head is varied superiorily and inferiorly, by a few degrees, in a sweeping fashion. This manoeuvre greatly increases the differentiation of spherical or near spherical structures from vessels. This plane of scanning visualises the following structures: the inferior vena cava, the right, middle and left hepatic veins, the hilar plate and the intra-hepatic confluence of the right and left branches of the portal vein (*Fig 3*), the hepatic artery, the right and left hepatic ducts including the primary confluence of the right hepatic ducts and portal vessels, and the branches of the same to segments I, II, and III. The extra hepatic biliary tree, portal vein and hepatic artery are visualised posterior to the inferior portion of segment IV. This completes the first sweep across the liver.

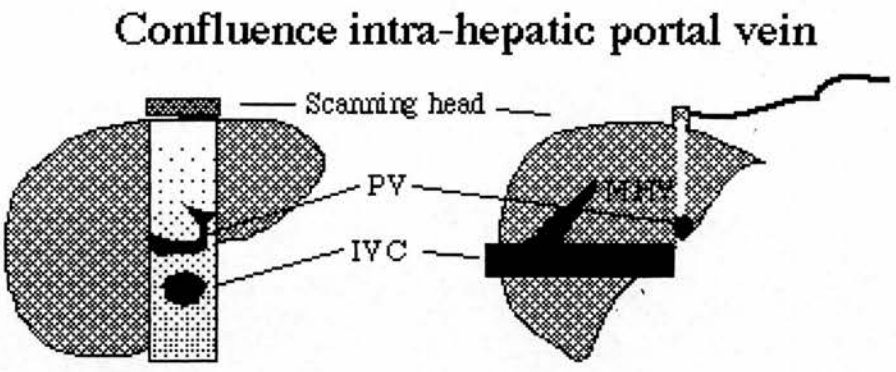

Fig 3. Showing the intrahepatic confluence of the portal vein (PV) and the branches of the portal vein to segments II and IV.

The probe is repositioned on the anterior surface of the liver superiorily abutting the right triangular ligament overlying the medial superior aspect of segment VIII and the right lateral aspect of segment IV (*Fig4 Plate 13*).

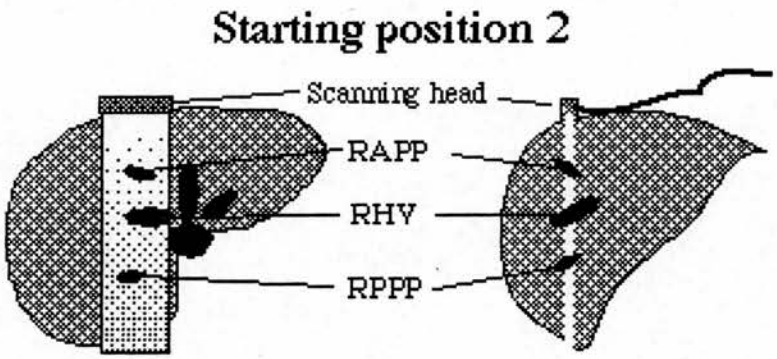

Fig 4 .To the right of the IVC visualising the right anterior (RAPP) and right posterior (RPPP) portal pedicle and the right hepatic vein.

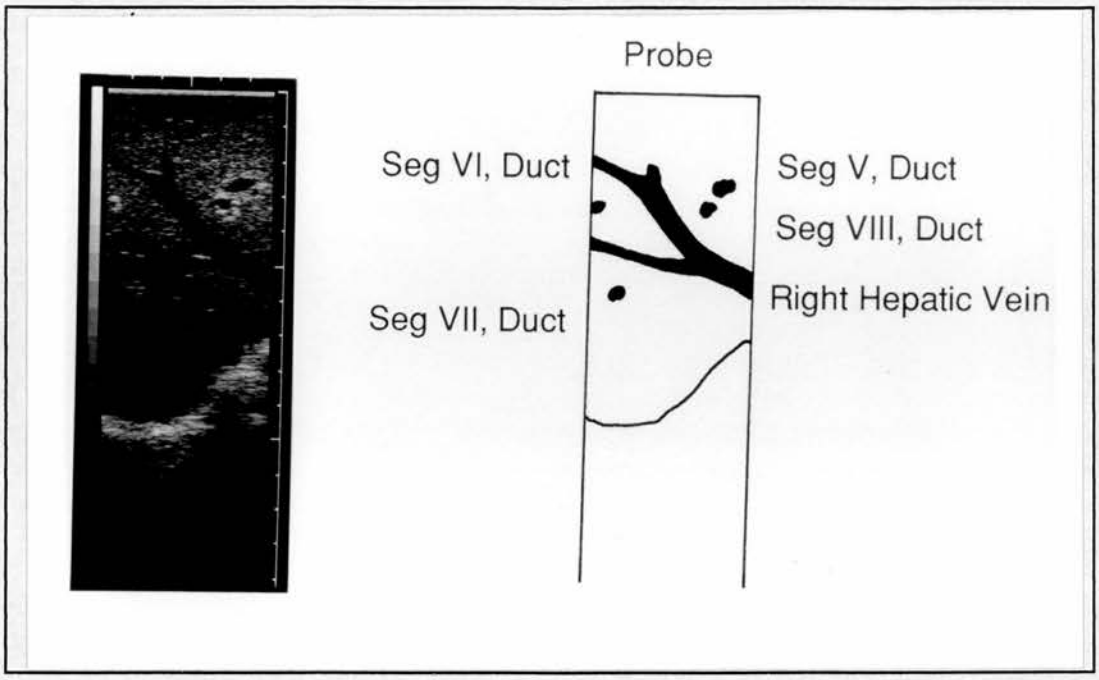

Plate 13. Starting position 2, with the probe head angled slightly to better show the right hepatic vein, the anterior portal pedicle has divided into the segment V and VIII branches and the posterior pedicle branches to segmentsVI and VII are bisected by a branch of the hepatic vein.

Again the position of the probe is confirmed in relation to the intrahepatic vascular anatomy. The left hand side of the scanning plane being in line with the right hand side of the inferior vena cava. With the probe in this starting position the head is angled superiorily until the plane of scan passes out with the substance of the liver superiorily. The plane of the scan is then returned to the vertical and the probe moved in an inferior direction across the anterior surface of the liver in a similar manner to the previous sweep. The anatomical structures visualised are: the middle and right hepatic veins, the anterior and posterior pedicals of the right portal tracts splitting into their segmental branches, the gallbladder and the right kidney posteriorly. The portal structures are seen again but from a slightly different viewpoint. The probe is then moved superiorily and to the right so that the left hand edge of the plane of scan is in line with the superior and inferior division of the anterior portal pedical. As the probe head passes more laterally with each scan so the natural curvature of the anterior surface of the liver becomes more pronounced. With the probe on the anterior surface of the liver in this position the plane of the scan

passes posteromedially instead of posteriorly as in the two previous sweeps. With the probe on the anterior surface of segment VII the head is angled superiorily and posteromedially and drawn inferiorly across the surface of segments VII and VI (*Fig 5*).

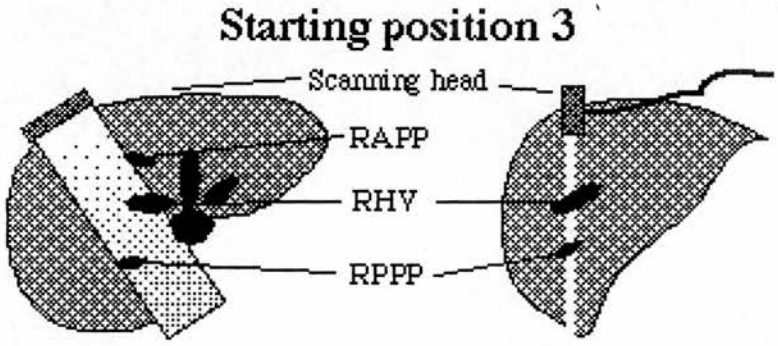

Fig 5 As the probe moves round the liver, the plane of the scan becomes more horizontal. This gives a constantly changing view of the portal structures and allows areas of interest to be viewed from more than one angle.

The structures seen are the lateral extension of the middle and right hepatic veins and the right kidney. The probe is then moved laterally and superiorily to lie over the posterior superior portion of segment VII. This puts the probe on the right lateral aspect of the liver with the plane of the scan almost horizontal. The head is again moved and angled as superiorily as possible and then returned to what is now a sagittal plane. The probe is drawn inferiorly as before, visualising the inferior vena cava, the middle and right hepatic veins, the anterior and posterior portal pedicles and the porta hepatis. In this way, all of the internal volume of the right lobe of the liver can be visualised from at least two different viewpoints. Any areas of interest can be further interrogated by moving the probe over the surface of the liver whilst keeping the area of interest in the field of the scan. This gives an opportunity to view the area of interest "from all sides" and assists in differentiating between subtle areas of acoustic shadowing caused by the normal intrahepatic structures and true areas of alteration of acoustic attenuation that might indicate diffuse malignant change. The left lobe of the liver is scanned in a similar manner with the scan head being moved to the left on each subsequent pass across the anterior surface of the lobe. The first superior to inferior pass identifies the superior portion of the

inferior vena cava, the middle and left hepatic veins and hepatic vein branches to segments IV, II (Plate 14) and III (Plate 15) in that order, the intrahepatic portion of the edge of the lesser omentum, the round ligament as it fuses with the left branch of the portal vein at its bifurcation into segment III and IV branches and the primary biliary confluence.

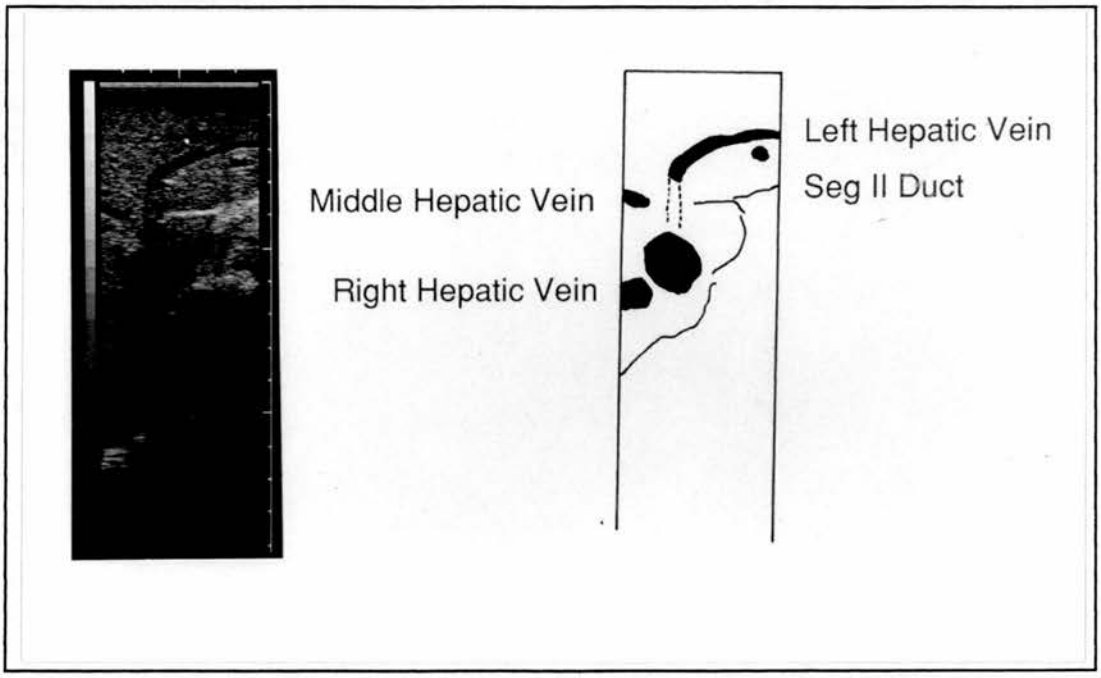

Plate 14. The segment 2 duct seen in relation to the left hepatic vein.

If the left lobe is small, a second pass more laterally over the lobe may visualise the remainder of segments II and III in some patients. When the lobe is large two further passes may be required.

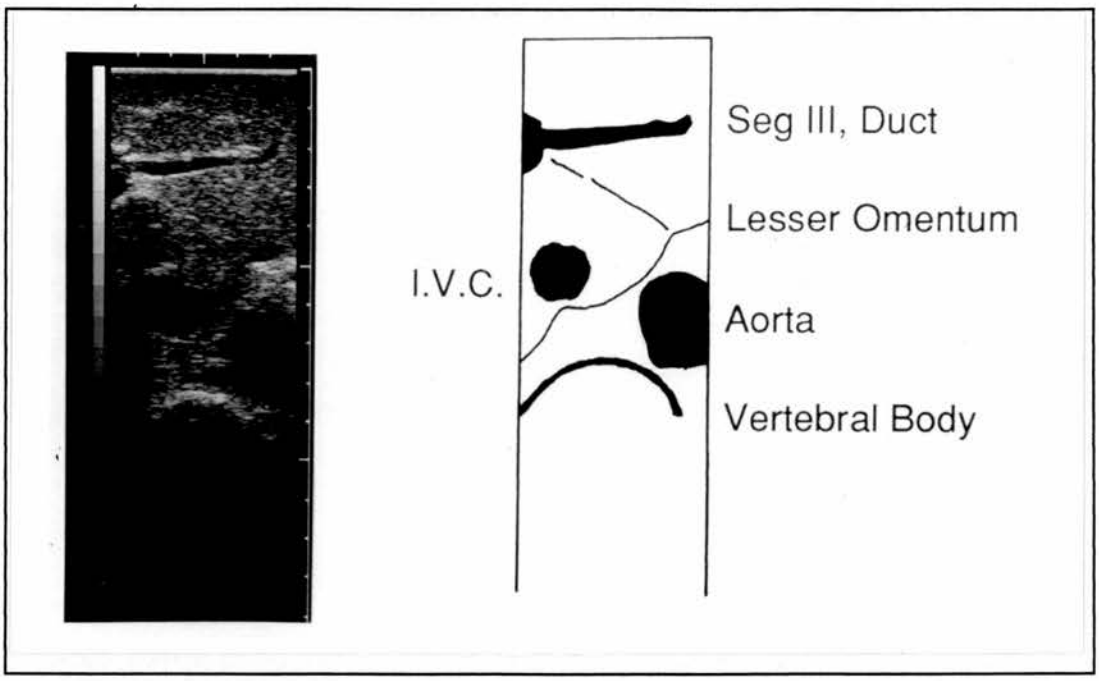

Plate 15. The segment III duct seen in relation to the edge of the lesser omentum.

Any lesions identified are recorded with regard to the segment of the liver in which they lie and to their size. It is possible to target lesions for 'Trucut' biopsy by identifying the lesion on ultrasound and then guiding the needle into the lesion by direct visualisation.

III.C.1.e. Postoperative sterilisation

After use, the ultrasound probe is washed under running cold water and sterilised for 15 minutes in a Cydex bath. The probe is then rinsed and stored non-sterile for future use.

III.C.2. Lesion identification on intra-operative ultrasound scanning.

Tumours in the liver are recognised by a number of features all or some of which may be present in any one tumour. A small percentage of tumours have an echogenic profile so close to that of normal liver that they cannot be recognised by their echo signature. These tumours may be detected by their volume effect, causing displacement of the normal intrahepatic anatomy.

Tumoûrs less than 5 mm present such a small image that they are difficult to detect even if they are echogenic. Tumour recognition is dependent on both the echogenic profile of the tumour, its size and its position. Tumours must also be differentiated from benign lesions within the liver and from variations of normal liver tissue.

III.C.2.a. Benign lesions

Hepatic cysts are the most common benign lesion seen on examination of the normal liver. They appear as spherical or near spherical areas of very low echogenicity, and may be present in any part of the liver. Most cysts contain serous fluid or bile which has an acoustic impedance close to that of blood and so may be compared to the blood vessels. Cysts however do not contain any movement artefact, which is often seen in blood vessels. Another feature is an enhancement of the image of the furthest wall of the cyst as compared to the nearest. Enhancement is caused by the relative reduction of the attenuation of the ultrasound signal as it crosses the fluid filled cavity of the cyst. Resulting in a relatively brighter reflection from the posterior wall of the cyst and also enhancement of the reflections from all structures posterior to the cyst. The effect of posterior enhancement increases with the size of the cyst.

III.C.2.b. Haemangiomas.

Haemangiomas are congenital areas of abnormal vascular development. They may occur at any site in the liver and may range in size from a few millimetres to many centimetres. Simple haemangiomas appear as areas of mixed increased echogenicity, signal reflection may be so great as to cast an acoustic shadow behind the lesion. Haemangiomas have a well defined margin and do not normally exhibit a hypoechoic halo. However, the appearance of a small haemangioma may exactly imitate that of a small tumour so as to be indistinguishable by routine ultrasonic examination alone. Haemangiomas may be defined by the use of an ultrasonic contrast agent such as carbon dioxide microbubbles; this technique is not in current clinical practice.

III.C.2.c. Nodular hyperplasia

Nodular hyperplasia is an area of abnormal growth within a normal liver. These areas of hyperplasia may have an ultrasonic appearance that can exactly mimic a hepatic tumour or a hepatic metastasis and so cannot be differentiated from tumour on the basis of ultrasonographic appearance alone. Nodular

hyperplasia is uncommon in the Scottish population.

III.C.2.d. Nodular regeneration in cirrhosis

Regenerating nodules in a macronodular cirrhosis may also give an ultrasonic appearance that is similar to an area of tumour or metastasis. The nodularity of micronodular cirrhosis is so fine as to be below the resolution of the ultrasound scanner but causes a generalised increase in the attenuation and reflectivity of the liver. The image of the liver appears brighter than the adjacent solid organs, particularly the right kidney.

III.C.3. Malignant lesions in the liver

A number of features when seen in relation to a lesion within the liver indicate malignant origin.

III.C.3.a. Hepatocellular carcinomas

When small, hepatocellular carcinomas tend to present as areas of decreased echogenicity. As they increase in size the core of the tumour becomes avascular and necrotic, the echogenic profile then changes. A hypoechoic rim appears associated with a central area of mixed echogenicity, some of which may be greater than the surrounding liver. When the central portion is of increased echogenicity there may also be some degree of posterior shadowing. Hepatocellular carcinomas tend to metastasise early via the intrahepatic portal circulation, producing a number of small daughter nodules. These may be seen in the portion of the liver supplied by one branch of the portal vein. Portal vein branches may be directly involved by the tumour and intra-vascular extensions of tumour thrombus are common and easily visualised. These two features seen together are characteristic of hepatocellular carcinoma. When very large, it may be difficult to compare the tumour to normal liver parenchyma. This problem can be overcome by using the split screen facility of the ultrasound camera to store a view of the normal liver against which the tumour can be compared (see chapter II Plate 1.).

III.C.3.b. Cholangiocarcinoma

Intrahepatic cholangiocarcinoma is uncommon, a more common occurrence is

the intrahepatic spread of cholangiocarcinoma from tumours occurring at the porta hepatis. These tumours are generally hyper-echoic and involve the extra hepatic portion of the biliary tree, arising from the bile ducts They are often diagnosed following a period of biliary obstruction. If this is the case there may be associated dilatation of the intrahepatic biliary tree.

III.C.3.c. Hepatic metastases from colon cancer

The appearance of these metastases is very varied and is to some degree dependent on their size. Features associated with colonic metastases are described here;

- Bull's-eye lesions are the most common appearance of hepatic metastases. They have a hypo-echoic rim and an iso-echoic or hyper-echoic centre. Lesions of this type tend to be 1 cm or larger in diameter and may occur at any position in the liver. They are near spherical in form until large, when they may take on a multi-lobulated appearance. They may be indented by an adjacent vessel or envelope the vessel, thereby causing its obstruction. (Plate 16, 17)

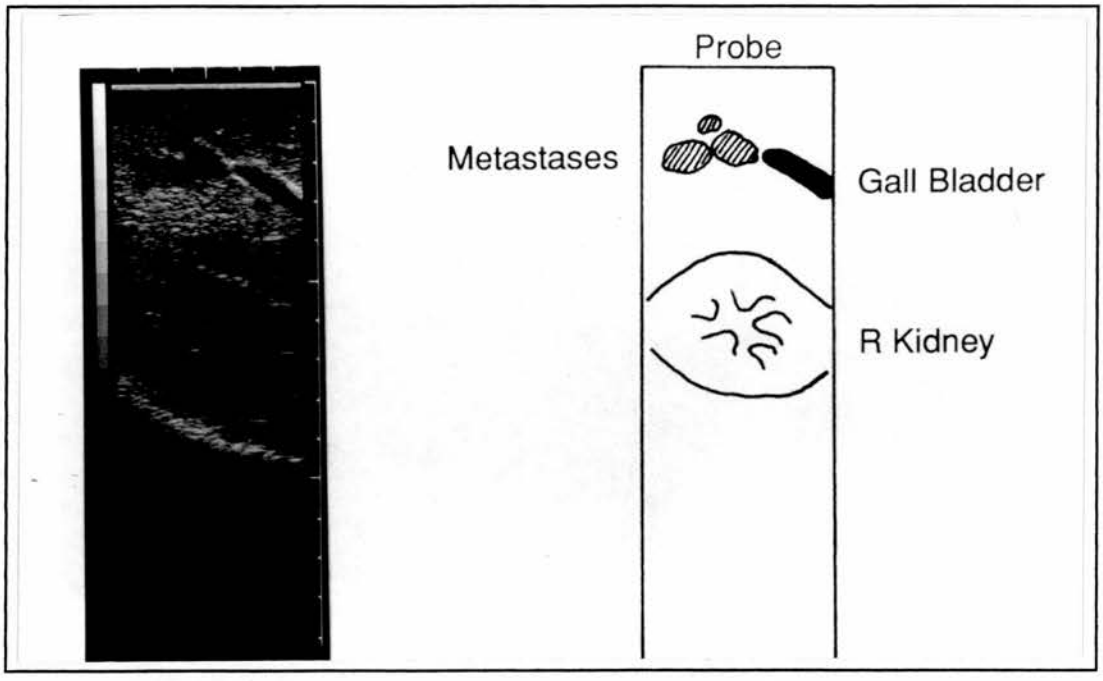

Plate 16. Three small bull's-eye metastases from a colon cancer related to the gallbladder bed.

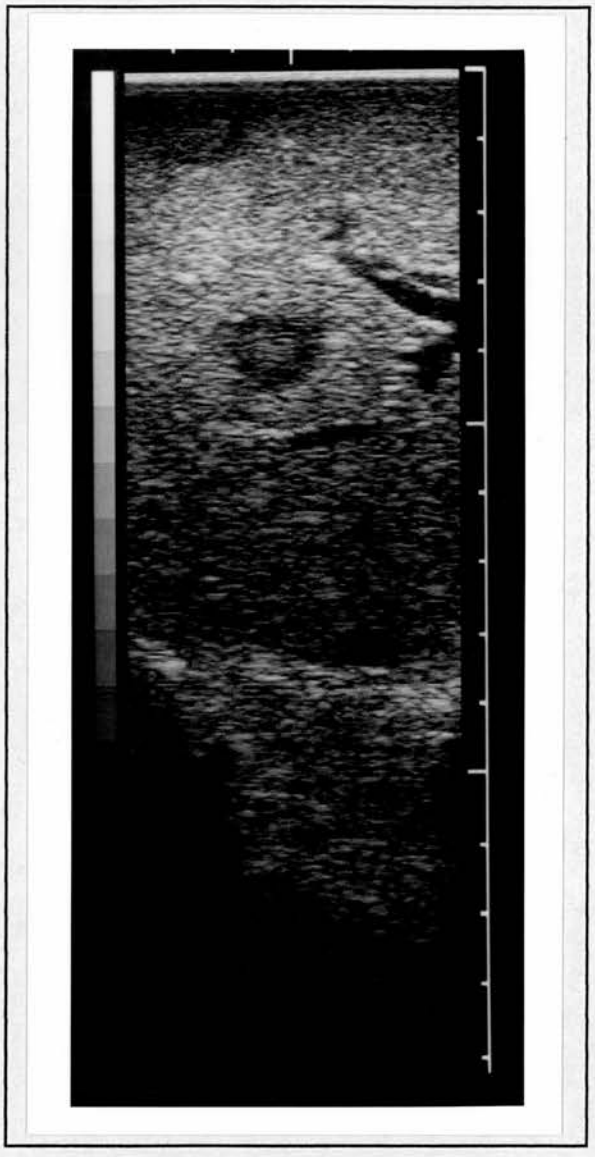

Plate 17. Solitary "Bull's-eye" metastases from colorectal cancer (centre of the plate). A second lesion is present at the top left hand edge of the plate. Both of these lesions are about 1 cm in diameter.

- Small hypo-echoic lesions which are spherical in form. These lesions are of a lower echogenicity than the liver but not as low as the intrahepatic vessels or cysts. They are uniform in echogenicity and may occur in any position in the liver (Plate 18).

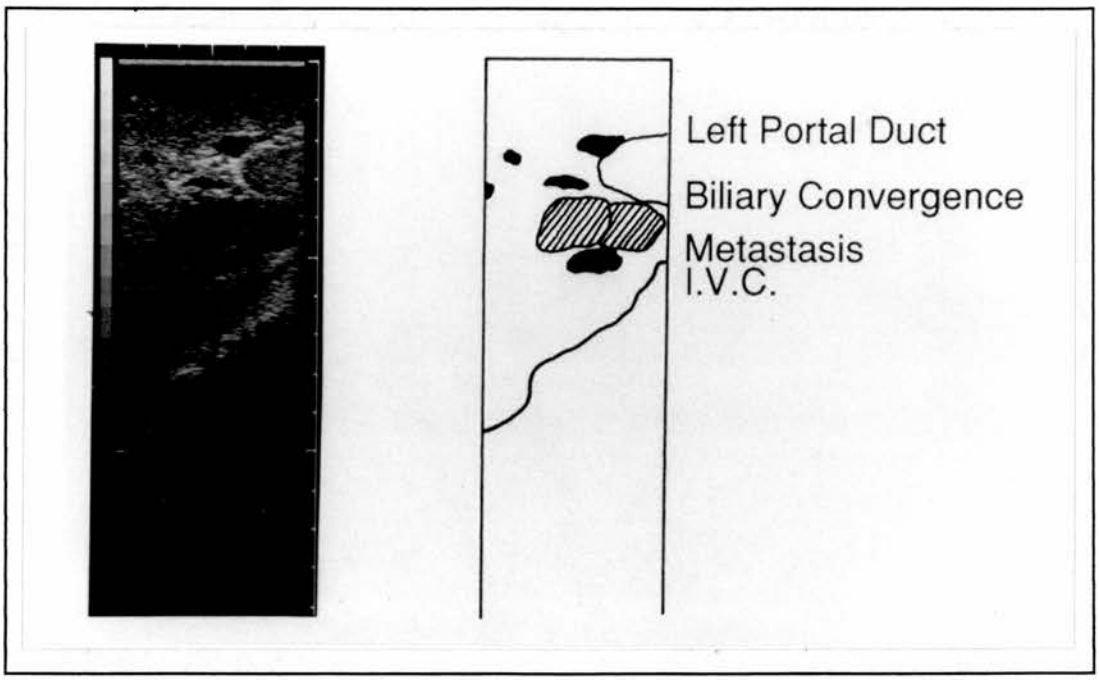

Plate 18. Two hypoechoic metastases lying anterior to the inferior vena cava.

- Iso-echoic diffuse involvement of the liver can occur when the metastasis has no clear margin. This type of metastasis can be very difficult to detect and if detected may be very difficult to delineate. The metastasis is of very similar echogenicity to the liver and has no outline, but can be recognised by very subtle changes in the parenchymal echo pattern or by a disturbance of the normal hepatic architecture. There may be an absence of small portal vein branches or the vascular anatomy may be distorted by the tumour. In some patients the only evidence of tumour is a change in the granular appearance of the liver parenchyma. These changes may be so subtle as to go unnoticed and may only be recognised in retrospect (*Plate 19*).

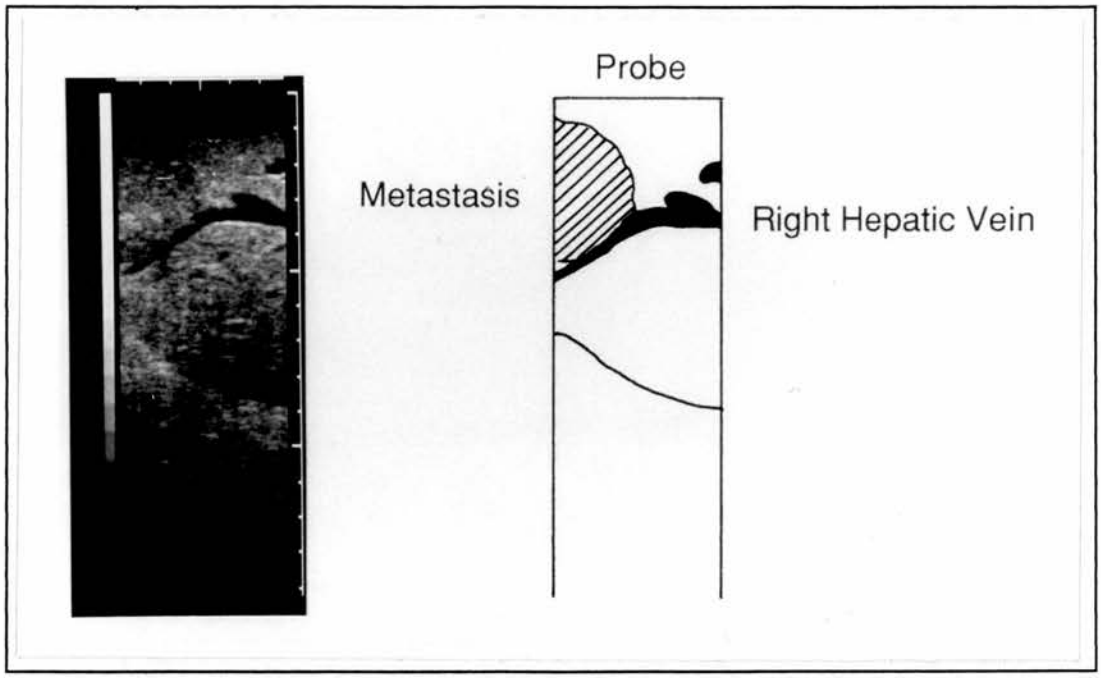

Plate 19. A near iso-echoic metastasis distorting the lateral portion of the right hepatic vein.

- Complex cysts with thickened irregular walls and internal septa may represent metastases from mucous producing colonic cancers. These cysts may be seen in association with bull's-eye lesions in the same patient. Cystic degeneration may occur in very large metastases and appears as a hyper-echoic lesion with a markedly hypo-echoic centre (*Plate 20*).

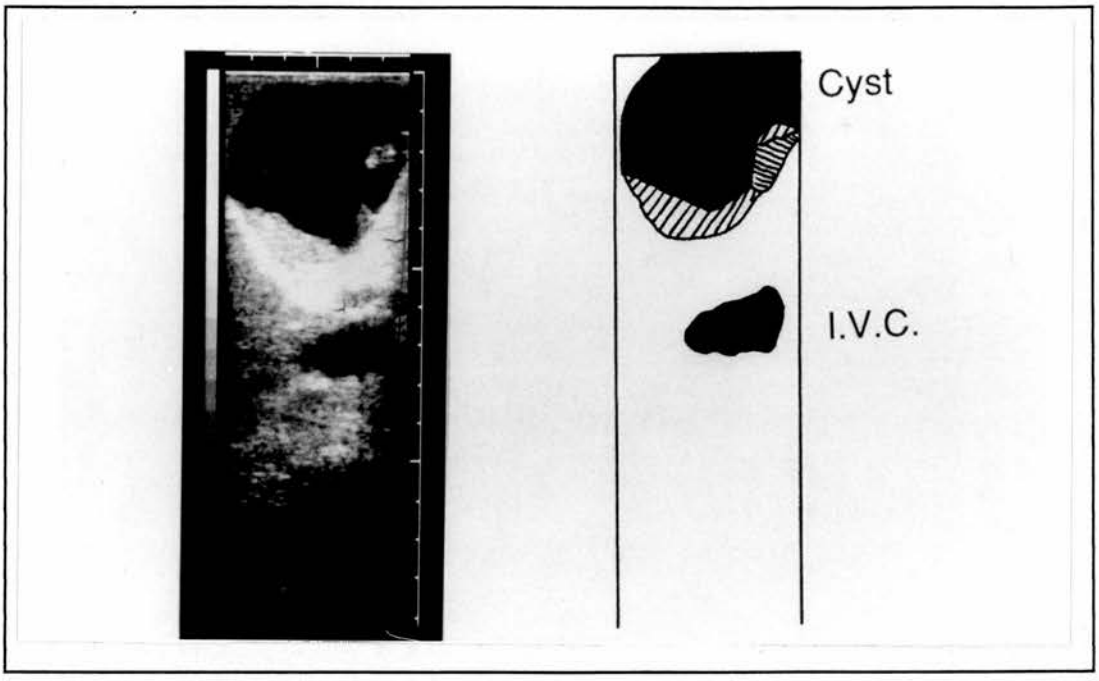

Plate 20. A complex cyst lying in segment IV. This scan is from the same patients as Plates 6, 7, 8, and 9. The scan shows the internal debris and septa.

III.C.3.d. Biopsy procedure.

A number of techniques are used in patients having resection of known hepatic metastases and in patients who are having resection of primary colon cancer.

In patients with known hepatic cancer biopsy is undertaken one of three ways;

Excision biopsy: after mobilisation of the liver and identification of the main tumour, if any other surface lesions of uncertain origin are seen they are excised in total. These samples are sent for immediate pathological identification by frozen section preparation.

Trucut biopsy: the needle tip is scratched with a scalpel to improve its echogenicity. It is then guided by the ultrasound image into the centre of the tumour and the needle closed. Ultrasonic guidance ensures that the biopsy actually comes from the lesion in question.

Fine needle aspiration cytology: this gives the smallest sample of cells to the

pathologist for diagnosis of the presence of malignancy. This technique is only used when either of the other techniques cannot be employed. Using a 22 gauge needle mounted on a 5 ml syringe, the tip of the needle is cross hatched by scratching with a scalpel blade and guided to lie within the lesion by ultrasonography. The plunger of the syringe is then withdrawn to create a negative pressure in the syringe and the tip of the needle moved back and forth in the lesion. The resultant small cores of tissue are smeared on to glass slides, air dried and fixed in alcohol.

The techniques used in patients with colorectal cancer were the same. In the majority of patients it was not possible to obtain either excision biopsy or Tru-cut biopsy within the confines of the study protocol which did not allow mobilisation of the liver or extension of the abdominal wound. In those cases where limited access was available, fine needle aspiration was the most commonly performed technique.

III.D. Selective Angiography

Selective angiography was performed on patients with potentially resectable liver metastases in order to delineate the internal arterial and portal anatomy of the liver and to identify the vascular anatomy of the tumours. In selected patients who had been found to have irresectable hepatic tumour therapeutic angiography with highly selective chemo-embolisation was performed.

III.D.1. Method

With the patient on the arteriography table, vascular access is obtained via a peripheral vein. The patient is sedated with 5-10 mg of midazolam. Using aseptic technique, arterial access is obtained in the right groin via the right common femoral artery using an arteriography sheath. The arteriography catheter is then inserted under fluoroscopic control. By intermittent injection of small aliquots of Niopam 300, to identify the arterial anatomy, the tip of the arteriography catheter is placed, via the coeliac axis and the common hepatic arteries, into the right or left hepatic artery. As the origin of the right hepatic artery may be from the superior mesenteric artery and the left lobe of the liver may less frequently derive part of its blood supply from the left gastric artery these vascular trees are defined by selective angiography of each vessel in turn. With the catheter in position, infusion is made via a computer controlled

syringe driver. The sequence of injection and exposure of the plates is computer controlled. Multiple sequences are obtained with contrast in the hepatic arterial tree.

Water-soluble contrast is injected at a rate high enough to cause an increase in the radio density of the arterial blood flow. Relatively high infusion pressures are required to overcome the internal resistance of the small bore arterial catheters and provide sufficient delivery of contrast to give an increase in density of the smaller branches of the arterial tree. At the end of the examination the access sheath is removed from the groin and the patient confined to bed rest with a pressure dressing applied for 24 hours.

This dynamic technique requires specialised equipment, considerable expertise in the performance of the investigation and in the interpretation of the resultant X-ray plates.

III.D.1.a. Contraindications

Arteriography was not performed in patients receiving anticoagulant therapy. Special care was exercised in patients with known peripheral arteriosclerosis as friable portions of intimal plaques within the arteries may be dislodged and cause distal embolisation. Patients with impalpable groin pulses were not suitable for angiography.

III.D.1.b. Reporting

The angiography films were all reported by a single consultant radiologist who performed all of the investigation in full knowledge of the findings of any other investigations that had been performed. Arteriography was not used as an investigation to detect new tumour but rather to detect the anatomical relationships of known tumours to the intrahepatic vascular tree and assess their resectability.

All of the investigations were carried out with the written informed consent of the patients.

Chapter IV

A comparison of preoperative ultrasonography, DBCT and IOE scanning in the determination of resectability of hepatic tumours.

IV.A.Introduction

IV.A.1. Staging

Prior to hepatic resection, the extent of intrahepatic tumour deposits and the presence of extra hepatic disease must be defined. The primary considerations in this regard are: the exact extent of the intrahepatic disease, the presence of local metastatic spread (transcoelomic, transhepatic), the presence of local recurrence of non hepatic, primary cancers and the presence of distant metastases (Baer HU, 1989; Eckberg H, 1987; Adson MA, 1987; Reinig JW, 1987; Nelson RC 1990). Although DBCT can be employed to stage intra-abdominal spread of disease, IOE scanning may improve the detection of intra-hepatic tumour. This chapter investigates the use of these two investigations in patients with known hepatic malignancy to establish whether IOE scanning can be used for the quantification and determination of resectability of intrahepatic malignancy.

IV.B. Aim

To compare DBCT and IOE scanning in the determination of resectability of hepatic malignancy by answering the following questions;

- Can DBCT alone be used to assess patients prior to hepatic resection ?

- Does IOE scanning detect more tumour than DBCT and if so how does this effect assessment of resectablilty ?

- Is IOE scanning as accurate as IOUSS in the determination of resectablilty of hepatic malignancy ?

IV.C. Patients

The series consists of patients referred to the Hepatobiliary Unit of the Royal Infirmary of Edinburgh over a 34 month period from January 1989. All of these patients had potentially resectable hepatic malignancies from a variety of primary tumours including primary hepatic cancers. Assessment was undertaken with a view to curative resection of the hepatic disease in all cases. The data were collected in a prospective manner onto a computerised database to enable comparison of the investigations. In those patients who underwent surgery, the results of the operative findings were compared with the preoperative staging investigations. There were 140 patients, 87 of whom were male with a median age of 59 years (range 52 to 82 years). The median age of the women was 61 years (range 25 to 84 years),

The underlying primary pathology in these patients is detailed in Table 1.

Site of origin	Number of patients
Colorectal	60
Primary hepatic malignancy	40
Biliary / Pancreatic	14
Ovary	3
Carcinoid	3
Lung	1
Gastric	1
Prostate	1
Breast	1
Brain	1
Cervix	1
Unknown	14
Total	140

Table 1. Primary pathologies in 140 patients presenting with hepatic metastases being staged prior to hepatic resection.

Of the 60 patients (38 male and 22 female), with colorectal cancer the median age was 60 (range 28-84 years). The stage of the primary tumour at presentation was Dukes "A" in 2, "B" in 17, "C" in 25 and "D" in 2. In 12 patients, the Dukes stage of the original tumour was not available. The mean time from primary operation to presentation was 652 days (4-6843). The longest disease free period of 18 years and 273 days occurred in a 56 yr. old man who had a sigmoid colon resection for a cancer of unspecified stage.

IV.D. Method

Patients were admitted to the Hepatobiliary Unit of the Royal Infirmary of Edinburgh. On admission a full history and examination was undertaken paying particular attention to signs of extra-hepatic malignancy. In a number of cases, preoperative abdominal ultrasound investigations performed in other hospitals were not repeated. All other investigations were undertaken at the Royal Infirmary of Edinburgh. Routine full blood count, urea and electrolytes, liver function tests and clotting screen were performed and a serum sample obtained for analysis of carcinoembryonic antigen and other tumour markers.

Each patient had a series of investigations performed to assess the extent and potential resectability of their hepatic tumour (*Fig 1.*). Not all of the investigations were performed in every case and the investigation algorithm was not always performed in this particular order.

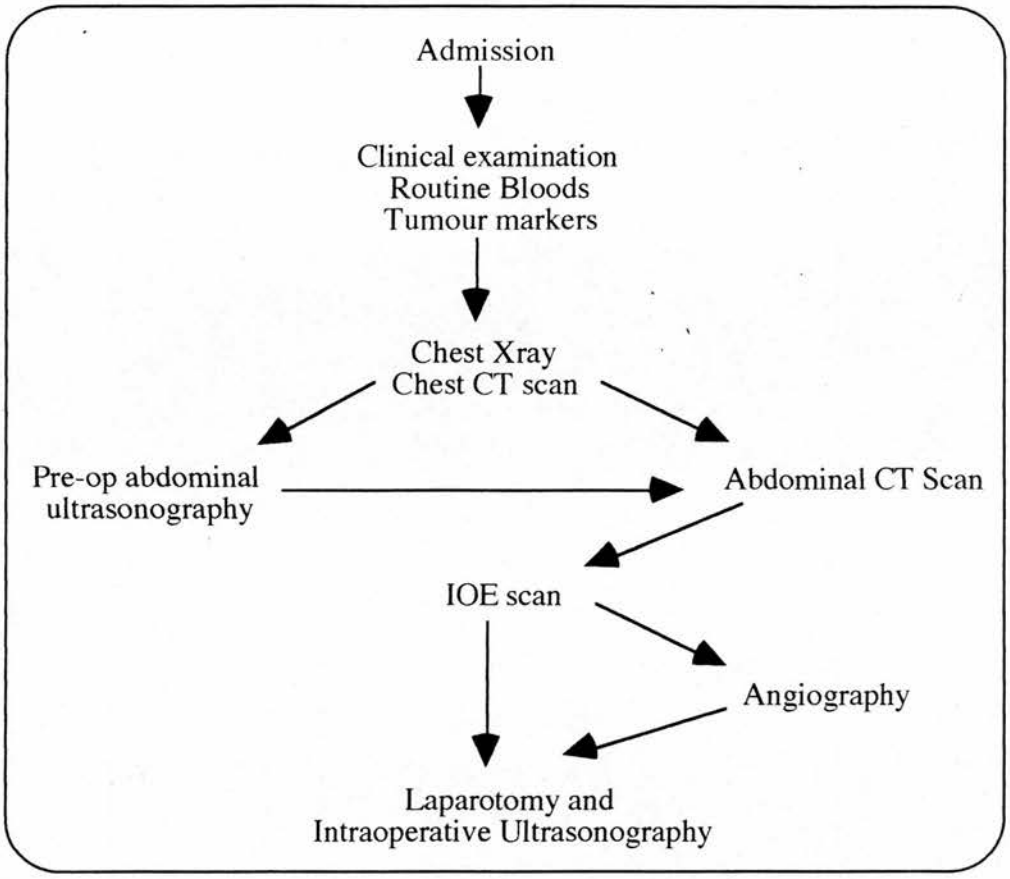

Fig 1. Sequence of investigation of patients with hepatic malignancy prior to operation

IV.D.1. Reporting of preoperative investigations

The investigations were reported in the following manner: the anatomical site of any metastases was described after Bismuth (1982). If a segment was in any way involved by tumour, it was recorded as positive. If a single metastases was reported as involving two or more segments then each of these segments was regarded as being positive for tumour. This method was adopted to give an accurate indication of the volume of liver involved by tumour and hence the volume of liver that would have to be resected to achieve a surgical cure. Patients have been considered to have inoperable disease by the following criteria;

- More than five contiguous segments of the liver involved by tumour.

- Tumour involving both the left (segments I-IV) and the right (segments V-VIII) hemi livers.

- Encasement of the inferior vena cava or the proximal hepatic veins at the vena cava.

- Tumour encasement of the confluence of the right and left portal tracts at the porta hepatis.

- Any evidence of extra-hepatic tumour.

IV.D.1.a. Operable disease

A tumour(s) was considered resectable, by extended right or left hemi hepatectomy, if it involved up to 5 segments in either the left (segments I-IV) or the right side of the liver (segments IV-VIII) with no evidence of tumour at any site outwith the liver. Multiple metastases were considered operable if they lay in 5 or less segments, in one side of the liver, or consisted of a single or less than four large metastases surrounded by multiple smaller daughter nodules.

IV.D.1.b. Inoperable disease.

Metastases were considered irresectable if they involved the porta hepatis and could not be removed without resection of; the primary biliary confluence or the primary bifurcation of the portal vein. If metastases involved the inferior vena cava and could not be resected with a 1cm clearance of normal liver they were not considered suitable for resection. Patients with primary hepatocellular carcinoma were considered irresectable if there was evidence of tumour thrombus extending into the portal vein. Patients who had evidence of any metastases outwith the liver were not considered for resection.

IV.D.2. Decision to operate

Following each investigation the results were reported and a decision made by the consultant surgeon (OJG), on resectability. If resection was feasible then a decision was made either to further investigate the patient, or proceed to laparotomy. At each stage, all of the information from previous investigations was re-evaluated and the decision to proceed made after its consideration. Angiography was used selectively in an attempt to more accurately define the operability of tumours in patients who had resectable disease on their other investigations. Patients who were considered to have resectable disease and were fit for general anaesthesia were subjected to either a laparotomy or

laparoscopy and hepatic ultrasonography. Contact hepatic ultrasonography undertaken at laparotomy and the these findings were considered to be the "standard" against which the preoperative investigations were assessed.

IV.D.3. At operation

At operation, laparotomy was undertaken by a bilateral subcostal incision. If obvious irresectable disease was present, no further hepatic mobilisation was undertaken. Laparotomy included visualisation and palpation of the primary site of the tumour, if this was intra-abdominal, followed by visualisation and palpation (as far as possible) of all of the peritoneal surfaces. If the initial laparotomy was clear then the liver was mobilised by division of the triangular and coronary ligaments. Bi-manual palpation and intra-operative ultrasonography was undertaken as previously described (Chapter III). In those patients who had laparoscopy performed with laparoscopic ultrasonography, the examination was undertaken in a similar fashion except palpation was not performed. All of the intraoperative / laparoscopic ultrasonography was performed by one surgeon (OJG). If patients went on to hepatic resection IOUSS was used to monitor the progress of the resection. If local palliation was required this was undertaken and the wound closed.

IV.D.3.a. Resection

Resection was undertaken with the CUSA ultrasonic hepatic dissector. The liver capsule was divided by coagulating diathermy current and then dissection was undertaken. During the dissection, progress was monitored using intra-operative ultrasonography. At the end of the procedure the specimen was sent fresh for pathological examination and photography by JP, University of Edinburgh Dept of Pathology.

IV.D.4. Analysis

The results of the preoperative investigations have been analysed with regard to the results found at laparotomy, excluding those patients who did not undergo laparotomy, and including all patients using the agreed stage of disease after all of the investigations had been reviewed. The outcome for patients who have remained in the Edinburgh area has been documented through follow up as an

outpatient. For patients living outside this area, follow up data has been collected from the referring consultant.

All of the paired, comparative, non-parametric data has been analysed using the 'Wilcoxon signed-rank test'. The actual calculation has been performed with the aid of 'Statview™ SE + Graphics v 1.03' (Abacus Concepts inc., 1984 Bonita Ave, Berkley, California 94704). Comparison of discrete variables in a series has been performed using the Chi sq. test and Four fold tables with 1 degree of freedom. These calculations have been performed by a program written for dBase III plus and published tables (Fisher and Yates).

IV.F.1.a. Morbidity

There was no physical morbidity associated with preoperative ultrasonography or preoperative DBCT scanning. The morbidity associated with IOE scanning has been investigated further and is analysed in chapter V. There were no complications related to intraoperative ultrasonography.

IV.E. Results

IV.E.1. Investigations performed

One hundred and forty patients had 600 investigations performed (*Table 2*).

Investigation	**Number**	**Operable (resected)**
Chest X-ray	101	
Thoracic CT scan	60	
Abdominal (DBCT) scan	118	60 (23)
Abdominal ultrasonography	112	60 (16)
Selective hepatic angiography	71	30 (25)
Iodised Oil Emulsion enhanced CT scan	74	36 (22)
Laparotomy / laparoscopy and IOUSS	64	64 (28)
Total number of investigations	600	

Table 2. The investigations performed prior to laparotomy in 140 patients with hepatic malignancy, the number of patients having each investigation, the number reported as operable, (the number finally resected)

IV.E.2. Preoperative hepatic ultrasonography

Preoperative hepatic ultrasonography (USS) was performed on 112 patients, the presence of tumour was confirmed in 101, of whom 60 were reported as having resectable disease. Of these 101, 30 patients went on to laparotomy for hepatic resection, 25 with an USS report of resectable disease and 5 with an USS report of irresectable disease. The presence of operable tumour was confirmed in 16 of the 25 patients and refuted in 9. Of the 5 with a report of irresectable disease, 4 had a successful hepatic resection, in-operability was confirmed in 1(*Fig 2*). Of the 11 patients who did not have tumour on their preoperative USS, 10 were found to have tumour by other investigations. The remaining patient, who had been referred from another hospital was found to have a simple cyst. In 32 patients the USS report defined inoperability in terms of the criteria detailed above .

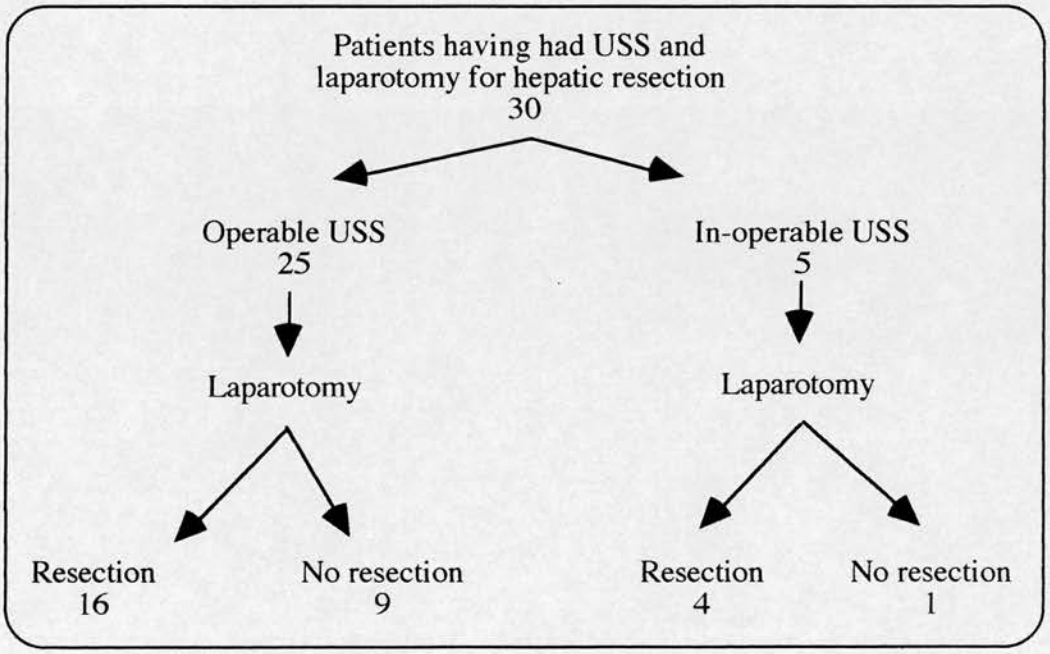

Fig 2. Algorithm for the investigation and treatment of patients who had preoperative ultrasonography and went on to laparotomy with the intention of performing hepatic resection

The results of USS in assessing operability of disease in the 30 patients who finally had a laparotomy are displayed in *Table 3*

Parameter	Percentage
Sensitivity	80%
Specificity	10%
Positive predictive value	64%
Negative predictive value	20%
Accuracy of	56%.

Table 3. Accuracy of preoperative ultrasonography in determining the resectablilty of hepatic metastases in 30 patients who underwent laparotomy.

Analysis can be made of these data considering all patients who had USS performed and their final outcome. There were 101 in whom USS confirmed the presence of tumour. The scan suggested operable disease in 60 patients and inoperable disease in 41 patients (the patient with a cyst has been excluded) (*Fig 3.*). Ultrasonography failed to detect intrahepatic tumour in 11 patients. Of the 60 patients with apparently operable disease, only 16 went on to successful resection. Of the 41 patients with inoperable scans, 4 went on to successful hepatic resection

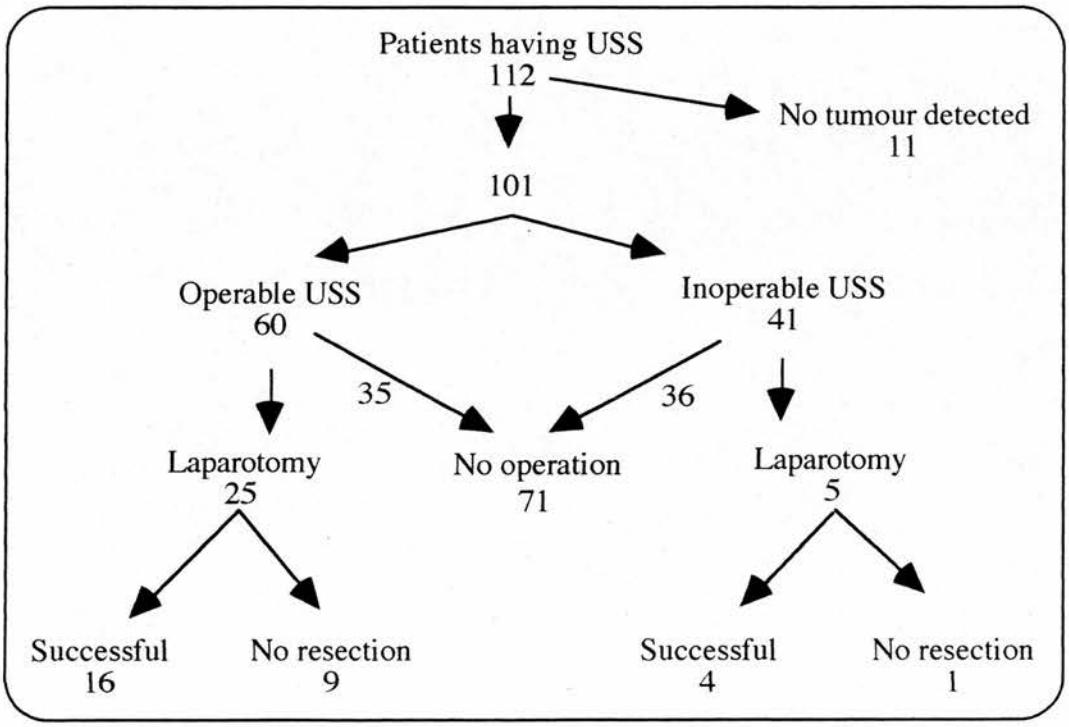

Fig 3 Algorithm for the outcome of all patients who had a preoperative ultrasound scan of the liver.

The overall results for specificity etc. of preoperative ultrasonography in detecting the presence of resectable disease are as follows (*Table 4*).

Parameter	Percentage
Sensitivity	80%
Specificity	46%
Positive predictive value	27%
Negative predictive value	90%
Accuracy	52%.

Table 4. The overall results of preoperative USS in determining resectability.

IV.E.3. Upper abdominal DBCT scanning

IV.E.3.a. Patients

One hundred and sixteen patients had DBCT scans performed the average age of the patients was 60 years (range 22-82 years). There were 73 men and 43 women. One hundred and eleven scans confirmed tumour within the liver. The primary tumours in the five patients who had undetectable metastases were: colon in 2 and one each from liver, biliary and lung. The primary sites of tumour in the patients with positive scans are listed below (*Table 5*).

Primary	Number of cases
Colon	45
Liver	36
Biliary	12
Lung	2
Small bowel	2
Gastric	2
Gynaecological	2
Breast	1
Unknown	9
Total	111

Table 5 Primary sites of tumour in patients having a positive DBCT scan as a staging investigation prior to resection of hepatic malignancy.

Sixty patients had operable disease on DBCT scanning, 23 of whom underwent successful hepatic resection. Of the remaining 51 patients who had

inoperable disease on DBCT scanning, none went on to successful hepatic resection. There were 2 patients who had no evidence of metastases on DBCT scan who had resectable tumour detected by other investigations.

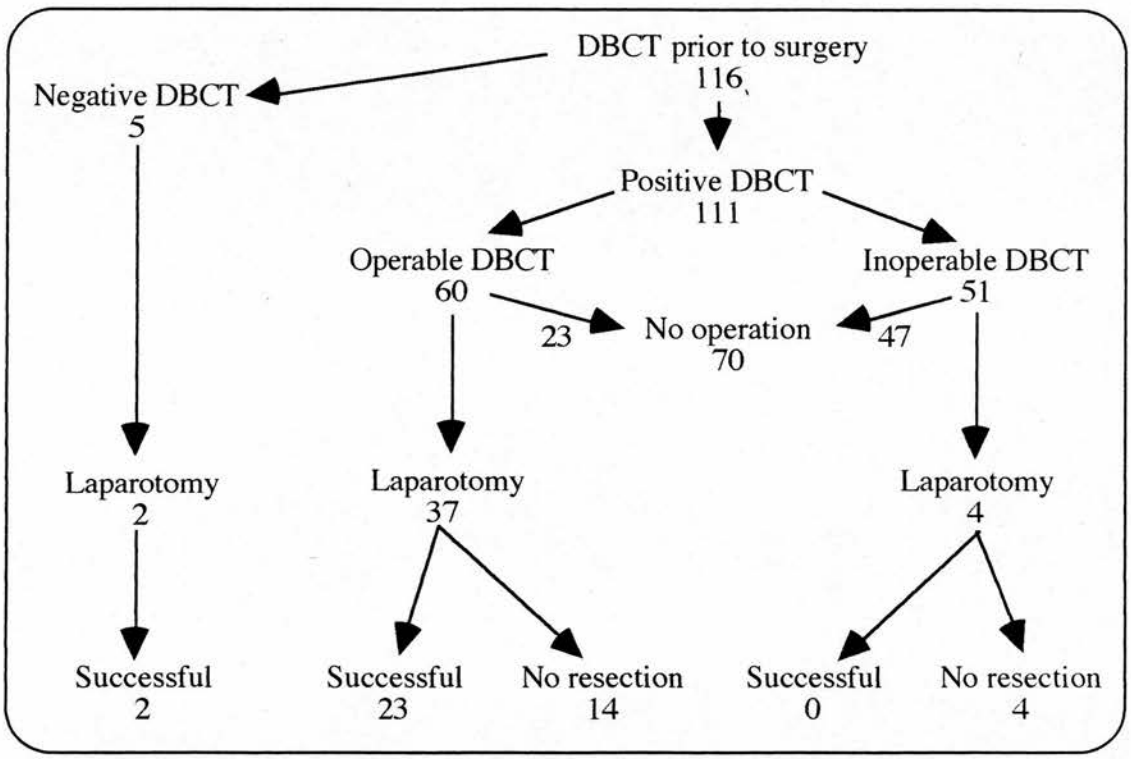

Fig 4. Outcome of 116 patients undergoing DBCT and being considered for hepatic resection.

DBCT scanning correctly predicted inoperability in all patients who had a laparotomy (and had inoperable disease on DBCT scan). There were 60 patients who had operable disease on their DBCT scans, of whom 37 underwent laparotomy and 23 had successful resection. Of 5 patients who had no evidence of tumour on DBCT scanning, 2 had successful resection of tumours (*Fig 4*). The overall results of DBCT in determining resectability of hepatic metastases in patients who had evidence of hepatic tumour on their DBCT scans are displayed in *Table 6* .

Parameter	percentage
Sensitivity	100%
Specificity	57%
Positive predictive value	38%
Negative predictive value	100%
Accuracy	67%

Table 6. Results of DBCT scanning in 111 patients with evidence of metastases on their CT scan. The 5 patients with no evidence of hepatic metastases have been excluded as resectability could not be determined from the negative scans.

IV.E.4. Iodised Oil Emulsion Enhanced CT Scans

IV.E.4.a. Patients

Seventy four patients had an IOE scan performed. Their average age was 58 years (range 22-78 years), 50 were male and 24 female. Forty one of these patients had primary colorectal cancer and 19, primary hepatic cancers (*Table 7.*).

Primary	Number
Colon	41
Liver	19
Biliary	6
Gastric	2
Small Bowel	2
Lung	2
Cervix	1
Unknown	1

Table 7 Site of primary tumour in 74 patients who had an IOE scan.

Of the 74 scans, 70 confirmed the presence of tumour, with 35 showing operable disease. Twenty two patients with operable scans went on to

successful resection. None of the 35 patients who had an inoperable scan went on to a successful resection. There were 4 patients in whom the IOE scan failed to detect any hepatic tumour, two of these went on to have successful resection of hepatic lesions (*Fig 5*). One of these two also had a negative DBCT scan. These four patients are detailed below.

Patient 1. 74 year old man with a previous history of resection of a Dukes B adenocarcinoma of the colon 6 months before the appearance of a hepatic metastasis on ultrasonography. CEA was moderately raised at 109 u/l. The metastasis was 1.8 cm in diameter lying in segment II. Curative left lobectomy was undertaken. This tumour was not seen by either DBCT or by IOE

Patient 2. 47 year old man with a previous history of resection of a Dukes C adenocarcinoma of the colon had a small centrally placed lesion detected by intra-operative ultrasonography. IOE scans, following chemotherapy, failed to detect the centrally placed lesion. Staging laparoscopy and laparoscopic ultrasonography were undertaken and the lesion was detected. Curative right hemi-hepatectomy was undertaken. Subsequent pathological examination revealed the lesion to be an area of nodular hyperplasia. The patient died with recurrent local, peritoneal and hepatic disease within 24 months of resection.

Patient 3. A 74 year old man presented with primary carcinoma of the gallbladder. CT scan failed to demonstrate any hepatic involvement, however intra-operative ultrasonography revealed the presence of tumour in segments IV and VIII. Curative right hemi-hepatectomy was undertaken with hepaticojejunostomy and roux-en-'Y' anastomosis.

Patient 4. In a 64 year old man with pancreatic carcinoma. DBCT scan performed at the referring hospital had revealed intrahepatic metastases, which were confirmed on arteriography as lying in segment II. The Arteriogram also showed involvement of the superior mesenteric vein and splenic vein by the primary tumour. The hepatic tumour was not seen on IOE scanning.

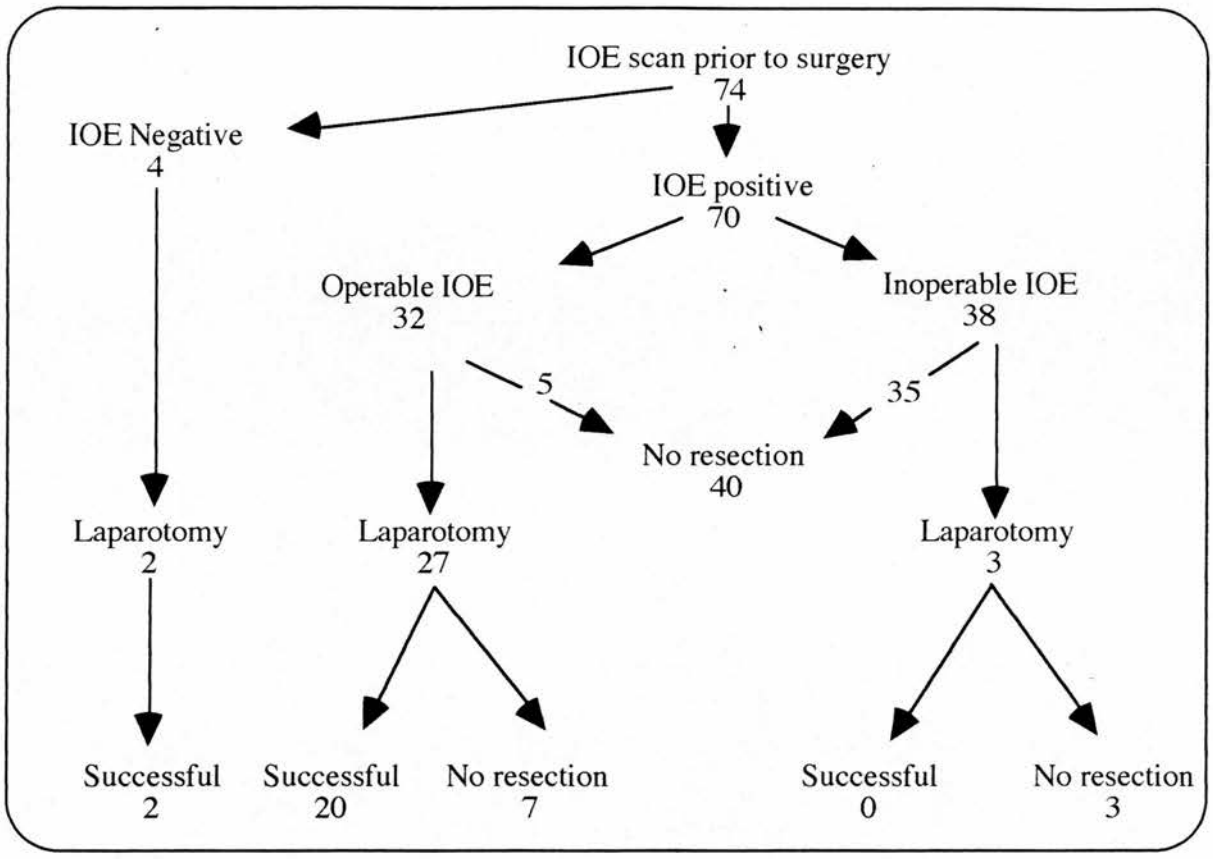

Fig 5. Outcome of 74 patients undergoing IOE scan and benig considered for hepatic resection.

The overall results for IOE scanning in determining resectability of hepatic tumours are tabled below (*Table 7*).

Parameter	**percentage**
Sensitivity	100%
Specificity	76%
Positive predictive value	62%
Negative predictive value	100%
Accuracy	83%

Table 7. Results of IOE scanning in 70 patients with evidence of metastases on their scan. The 4 patients with no evidence of hepatic metastases have been excluded as resectability could not be determined from the negative scans.

The details and the reasons for hepatic resection not being performed in the 7 patients with apparently operable IOE scans were as follows:

Patient 1: A 57 year old man with a previous resection of a Dukes B carcinoma of the colon. IOE scan suggested resectable metastases limited to segments II and III. These findings were confirmed at laparotomy but extensive coeliac nodal involvement by metastatic adenocarcinoma precluded resection.

Patient 2: A 71 year old man with a primary hepatoma in segment III, IV and V on IOE scanning. Found at laparotomy to have involvement of the falciform ligament and the anterior abdominal wall.

Patient 3: A 62 year old woman with prior resection of a Dukes B carcinoma of the colon. IOE scan suggested resectable metastases in segments V, VII and VIII. She was found to have multiple bilateral hepatic metastases at operation.

Patient 4: A 56 year old woman with prior resection of a Dukes C carcinoma of the colon. IOE scan suggested resectable disease in segments IV, VI, VII and VIII. At operation more extensive disease found in the right lobe involving the I.V.C. and the porta hepatis.

Patient 5: A 66 year old man with previous resection of a Dukes A carcinoma of the colon. The extent of intrahepatic disease found by IOE scanning was confirmed at operation. The peritoneal surfaces were, however, studded with adenocarcinoma and there were portal lymph node metastases.

Patient 6: A 55 year old woman with a hepatic metastasis from a lieomyosarcoma of the colon. IOE scanning failed to detect direct extension of the hepatic metastasis into the anterior abdominal wall.

Patient 7: A 59 year old man with a hepatoma in the right lobe of the liver. IOE scanning failed to delineate a large metastasis in the right adrenal gland.

IV.E.4.b. Pulmonary metastases

There were 16 patients with pulmonary tumour in this series. One hundred and one patients had a chest X-ray (CXR) performed and 60 patients had a CT scan of the thorax. Seven tumours were detected in the 101 patients by CXR. Twelve tumours were detected in 60 patients by CT of the thorax. In 50 patients who had both investigations, CXR detected only 3 of 11 tumours present on CT (Chi sq. = 5.32 1df, $p < 0.05$) There were no false positive investigations.

Although the specificity and accuracy of CXR in the detection of pulmonary metastases were high (100% and 84% respectivly) its sensitivity was poor (27%) CT scanning of the thorax detected all of the thoracic tumours which were known to be present. It should be noted that these results have not been validated by any other investigation, however, no patient has presented pulmonary metastases during the follow up period. .

IV.E.5. Angiography

Arteriography was performed in 71 patients with a mean age of 60 years; the series contained 48 men. The examination revealed operable disease in 30 patients, 20 of whom eventually underwent successful hepatic resection. Forty four patients had both an IOE scan and arteriography performed, 28 of whom had operable disease on their IOE scan. Arteriography correctly predicted resectability in 17 and IOE correctly predicted resectability in 19 of the 20 patients who had a successful resection. Of the 24 who did not undergo successful resection, irresectable disease was predicted in 19 by arteriography and in 15 by IOE scanning. In the 44 patients who had both arteriography and IOE scanning, arteriography had a sensitivity of 85%, specificity of 79%, positive predictive value of 77%, negative predictive value of 86% and an overall accuracy of 82% compared with 95%, 62%, 68%, 94%, and 77% respectively for IOE scanning. The arteriograms were reported with full knowledge of the IOE scan results and did not significantly improve the accuracy of the investigation (Chi sq = 0.3 1df $p > 0.5$).

IV.F. Comparison of DBCT and IOE by detection of involved segments.

A direct comparison has been made between IOE and DBCT scanning in the number of hepatic segments found to be involved by tumour by each investigation. All of the DBCT and IOE scans were reported with regard to the number of liver segments involved by tumour rather than the number of metastases present. There were 66 patients who had both investigations performed (*Table 8*).

Patient group	numbers	Segments detected IOE	DBCT	Significance
All patients	66	200	139	p = 0.0001
Colorectal cancer	33	96	66	p = 0.0002
Primary Hepatic cancer	16	55	35	p = 0.0006
Other cancers	17	49	38	p = 0.0067

Table 8. Comparison of the number of segments detected by DBCT and IOE scans in patients having both investigations. Statistical analysis by Wilcoxon signed rank.

Overall DBCT detected 94 involved segments in the right hemi liver (segments V, VI, VII, VIII) and 45 in the left hemi liver side (segments I, II, III, IV), IOE detected 123 involved segments in the right and 77 in the left. Patients with metastatic disease were more likely to have tumour in the right liver than the left compared to those with primary hepatic malignancy. In the 33 patients with metastatic colorectal cancer, DBCT identified 54 segments in the right liver and 12 in the left (p = 0.0001). IOE detected 67 segments in the right liver and 28 in the left (p = 0.002). In the 16 patients with primary liver tumours DBCT detected 18 involved segments in the right and 17 in the left (p = 0.5) where as IOE detected 28 segments on the right side and 27 in the left hemi- liver (p = 0.7).

In the 66 patients assessed by both DBCT and IOE the hepatic lesions were deemed to be resectable by DBCT in 41 patients; 18 (44%) of these underwent successful resections. Nineteen (66%) of the 31 patients shown by IOE to have resectable disease went on to successful resection. The false positive rate for resectablilty was 34 % for DBCT and 18 % for IOE.

Thirty-four patients underwent operative assessment of the liver either at laparotomy or at laparoscopy. In these patients there was 90% concordance in the number of segments involved per patient, intraoperative ultrasonography detecting 84 involved segments, 76 of which had been detected by IOE. DBCT detected only 63 segments in the same patients. There was no significant difference in the number of involved segments among the three investigations in these patients.

IV.F.1. Comparison of USS, DBCT and IOE

All three preoperative investigations, USS, DBCT and IOE were performed and detected the metastases in 49 patients. The accuracy has been calculated for each investigation in determining the resectability of these metastases (*Table 9*).

Results	USS	DBCT	IOE
True positive	12	16	16
True negative	11	18	25
False positive	22	15	8
False negative	4	0	0
Parameter (expressed as %)			
Sensitivity	80	100	100
Specificity	46	57	76
Positive predictive value	27	38	62
Negative predictive value	90	100	100
Accuracy	52	67	82

Table 9. Comparison of preoperative USS , DBCT and IOE scanning in the assessment of operability of hepatic tumour.

IOE scanning is more accurate than USS (Chi sq = 14.56 1df, $p < 0.001$) in the determination of resectability in patients with hepatic malignancy. DBCT is also more accurate than USS (Chi sq = 5.07 1df, $p < 0.05$). There is no significant difference between IOE scanning and DBCT scanning in the determination of resectability (Chi sq = 2.78 1df, $p > 0.1$).

IV.F.1.b. Relation of duration of symptoms to resection

The period of time between primary resection and presentation with hepatic metastases in patients with colorectal cancer bore no significant relationship to the likelihood of the metastases being resectable. The median lag time for

patients who did not undergo a resection was 312 days and for those who did was 204 days; this difference did not reach significance using the Mann-Whitney U test.

IV.G. Discussion

IV.G.1. Exclusions

Patients in this study were being investigated in a clinical setting and so their management was altered during the course of their investigation as more information became available. Patients with pulmonary metastases on CXR were not subject to angiography or IOE scanning as this would have exposed them to the risk of investigation-induced morbidity with no possible benefit. Thus there is a possibility of bias caused by the exclusion of patients from further investigation on the basis of one of the previous investigations. Patients undergoing the second and subsequent investigations are selected groups. The two principle comparisons have been made between the patients who had both DBCT and IOE scans performed and patients who had DBCT, IOE and USS performed.

IV.G.2. Chest X ray

When patients are considered for hepatic resection it is important to exclude dissemination to other sites. In this series, CXR alone detected metastatic disease in 7% of all referred patients. In the 50 patients who had both investigations, CT scan of the thorax revealed metastases in 22% of patients compared to 6% detected by CXR. Overall, 11% of our patients had pulmonary metastases at the time of referral. In 39 patients, no CXR had been performed prior to referral, 24 of these were secondary referrals from other hospitals. The high incidence of pulmonary metastases in patients with hepatic metastases makes accurate imaging of the lungs as important as hepatic imaging (Sugarbaker PH, 1990). The PA chest radiograph is not as sensitive or as accurate as a CT scan of the chest and this has been confirmed by our own experience.

IV.G.3. Ultrasonography

Considering the 101 patients who had an USS which detected tumour; the investigation did not provide reliable information regarding the resectability with a positive predictive value of only 27% and an overall accuracy of 52%. The high sensitivity (80%) is to be expected as almost all of the patients in this series were selected for assessment on the basis of previous ultrasonographic evidence of hepatic tumour. The low accuracy of USS in determining resectability is also expexted. The preoperative detection of hepatic tumours by ultrasonography is extremely variable and shown to range from 42% to 90% (Machi J, 1991; Clarke MP, 1989). Although smaller metastases are frequently missed because they are out of the range of resolution of the echo camera, larger tumours in the superior part of the right lobe may also be missed because of the lack of a sonolucent window through which to view them. This problem may be compounded by obesity in some patients.

Taking the series as a whole, ultrasonography has a high negative predictive value for operability of 90% . By refining the reporting of USS to document the number of distinct metastases, the involvement of the porta hepatis and the presence of bilateral disease, USS could be used to exclude patients with inoperable diseases from further investigation. Although there were 80 patients, with irresectable disease who had a detailed USS report, only 32 of these contained information relating directly to the exclusion criteria for resection used in the study. The specificity (33%) and positive predictive value (35%) of USS in this study are too low identify which patients will ultimately have resectable disease, this has been shown by others (Sugarbaker PH, 1990; Adson MA, 1987).

Ultrasonography is used in a clinical context to screen patients for the presence of hepatic metastases following surgery for malignant disease, with a view to curative intervention if possible. Unfortunately hepatic metastases large enough to be detected by this USS are likely to be irresectable at the time they are identified, in this series only 28 of 140 patients (20%) eventually had successful hepatic resection. Patients who are suspected of having metastatic disease but have no tumour detected by USS should be further investigated. However Those, who are demonstrated to have irresectable disease by USS should only be investigated further if there is good reason to suspect the USS report is inaccurate. Ultrasonography is an excellent screening tool to reduce the number of patients with irresectable hepatic tumour going on to further investigation. Its main advantages are high negative predictive value, safety,

the ease of the investigation, general availability and low cost.

IV.G.4. DBCT scanning

In the 49 patients who had both USS and DBCT, DBCT increased the accuracy of assessment of resectability of hepatic metastases from 52% to 67% and reduced the false positive rate to zero. DBCT scanning has been shown by others to be less accurate than ultrasonography in the detection of hepatic malignancy (Sheu J-C, 1985; Gozzetti G, 1986;). Castaing showed an equal accuracy of 68% for ultrasonography and 67% for CT scanning (Castaing D,1986). Others have shown that CT is more accurate than ultrasonography (Schreve RH, 1984; Alderson PO, 1983). However, none of these series have compared the accuracy of the investigations in assessing resectability, rather than the simple detection of metastases.

DBCT consistently underestimated the number of liver segments involved with tumour when compared to both laparotomy with contact hepatic ultrasonography and IOE scanning. If DBCT scanning were the only investigation used to determine resectability prior to surgery the rate of laparotomy for irresectable disease would have been 62%, an unacceptably high figure. Although DBCT scanning is able to detect intrahepatic malignancy, 11 patients had more extensive irresectable intrahepatic disease than had been identified by the DBCT scan. This suggests that DBCT scanning is too insensitive to be used to determine the resectability of tumour. DBCT scanning however detected tumour in 111 of 116 patients (96%), correctly diagnosing irresectable disease in 51 with an accuracy of 100% . This suggests that DBCT scanning is an excellent tool both when screening for metastases and for excluding patients with extensive disease from further investigation.

IV.G.5. IOE scanning

IOE scanning is a non-invasive, repeatable and safe technique and was the most powerful of the preoperative investigations in the assessment of the resectability of hepatic malignancy. IOE scanning correctly determined resectability in 74% of the patients who came to laparotomy and had an overall accuracy in determining resectability of 82%. This improvement was due to

the increase in the detection of segments involved by tumour. Lewis et al showed a 38% increase in the number of metastases detected by EOE-13 enhancement over DBCT, comparable to the 43% (61/139) increase in the number of involved segments in this study (Lewis E, 1982), while Reinig et al. showed a 41% increase in lesion detection for EOE-CT over unenhanced CT scans (Reinig JW, 1987). IOE has considerable advantages in that it can be administered outside the CT room prior to the examination. The enhancement is predictable and has not failed in this series. The addition of IOE to CT scanning did not improve the detection of peritoneal spread of tumour. In particular IOE scanning did not effect the appearance of intra-abdominal lymph nodes or peritoneal seedlings.

All of the patients in this series were premedicated with hydrocortisone. A small number of patients experienced mild side effects following the IOE infusion, these were self limiting in all cases. IOE is phagocytosed from the circulation by macrophages throughout the body, whilst the largest concentrations of tissue macrophages are in the liver and spleen, smaller number are present in the lungs and bone marrow. Tissue macrophages digest the phagocytosed material, present portions of the phagocytosed material at cell surface receptors complexed with RNA to aid immunological recognition and via cell surface receptors cause activation of the complement cascade. It is likely that the latter of these, the non-specific activation of the complement cascade, may be responsible for a number of patients feeling "flu like" following the investigation. The reactions to the infusion have been documented in Chapter 5. The side effects experienced did not limit the use of the investigation on patients prior to resection. Previous problems with severe reactions to the contrast agent in 4% of patients (Miller DL, 1984) have not been apparent when used in the way described above.

Overall IOE scanning was the most accurate (82%) and specific (76%) preoperative investigation and had the highest predictive value (62%) for the resectability of tumour. However, if IOE were the only investigation used prior to resection, 38% of patients would have been subject to laparotomy for irresectable disease. IOE scanning and DBCT scanning were not complementary, there was no advantage in performing both investigations. Neither investigation can detect small-volume extra hepatic intra-abdominal disease: inability of CT and IOE scanning to detect this type of disease is a major and apparently insurmountable limitation of these techniques.

These data were collected before CT portography was popularised in Britain

(Goulet RJ, 1990; Nelson RC, 1990; Matsui O, 1987). CT portography was not being performed in Edinburgh at the time of this study. Indirect comparisons between IOE and CT portography have been published and show very similar levels of accuracy (Goulet RJ, 1990). CT portography however, has a number of potential disadvantages, the need for arterial cannulation, CT portography is labour intensive in the placement of the arterial catheter requiring an experienced vascular radiologist. If there are vascular anomalies the catheter may have to be repositioned during the scan. Finally portography is a dynamic investigation and is prone to false positive results because of perfusion defects and flow anomlies within the liver. Further direct comparisons of these two techniques within a clinical setting will be required to determine which is the investigation of choice.

A major advantage of IOE scanning is that it can be performed in any radiology department with access to a CT scanner. The emulsion in its present stage of development is stable in storage and has few side effects and the administration of the emulsion requires a minimum of equipment. The technique is robust and has been used as an experimental tool in our department without problems. Utilisation of this technique could allow accurate assessment of liver tumours to be obtained in District General Hospitals with equipment which is already available and without the need for particular radiological expertise.

IOUSS

In those patients who were subjected to laparotomy, it appeared that intraoperative ultrasonography was as accurate as the preoperative investigations in the assessment of hepatic malignancy. IOUSS detected tumour in a greater number of hepatic segments but this did not reach significance. IOUSS also gave information as to the exact vascular involvement and the precise segmental anatomy of each metastases. Of those patients who appeared to have resectable metastases on IOE scanning, 33% had irresectable disease, 28% of whom had an intrahepatic component. This suggests that IOE scanning, though better than USS, still tends to underestimate the extent of hepatic involvement. Because of the small numbers of patients these differences did not reach statistical significance.

Intraoperative ultrasonography has a number of advantages over IOE or DBCT scanning. The ability to accurately assess the vascular relationships of tumours, the proposed resection margins and to exclude the presence of even very small occult metastases makes intraoperative ultrasonography imperative

before finally committing the patient to a hepatic resection. The major limitation of IOUSS in the past has been the prerequisite of laparotomy, this has been superseded by laparoscopic IOUSS. Laparoscopic IOUSS has all of the advantages of IOUSS without the need for laparotomy.

IOE scanning is the most accurate preoperative investigation prior to hepatic resection and so could be considered the "Gold Standard" against which any other techniques can be compared.

Given the considerable advantage of IOE scanning over DBCT, it appeared that this investigation could be used to more accurately stage the liver involvement of patients undergoing curative resection of primary colorectal cancer. Previous data based on operative ultrasonography and/or CT scanning following curative resection of colorectal cancer (Finlay IG, 1986: Machi J, 1987: Olsen AK, 1990; Gunven P, 1985; Davies AH 1990) has suggested that up to 30% of patients have metastases present at the time of operation. Only a proportion of these are detectable by palpation and the remainder are occult. IOE scanning could be used to improve the detection of occult metastases following colonic resection for cancer.

Chapter V

IOUSS and IOE scanning in the screening of patients undergoing resection of colonic malignancy for hepatic metastases.

V.A. Introduction

Accurate staging of colorectal cancer at the time of surgery is important, particularly as the presence of hepatic metastases is the most powerful determinant of outcome in the first two years following curative primary resection (Cady B, 1970; Wagner JS, 1984; Arnaud JP, 1984.). Hepatic metastases may not be clinically apparent either by pre-operative hepatic imaging or palpation at operation. Such occult metastases remain as powerful a factor in the determination of outcome as detectable lesions (Finlay IG, 1983; 1986). Impalpable (occult) metastases may be detected by DBCT or IOUSS (Finlay IG, 1983; Charnley RM, 1991). and so it is questionable if more advanced preoperative staging, requiring prolonged hospital stay and incurring cost, is of value for patients who in any event require a laparotomy for the treatment of their primary pathology. Such patients may be candidates for intraoperative staging by IOUSS alone. Although detecting metastatic disease at the time of operation will not obviate the need for surgery, it may modify the planned surgical procedure from high risk, radical primary surgery to palliation with lower risk but incomplete local resection.

IOUSS has been shown to be of value in hepatobiliary practice (Bismuth H,1987; Makucchi M,1987; Soyer P, 1992; Sheu J-C, 1985; Castaing D, 1985; 1986; Gozzetti G, 1986; Sigal B, 1982; 1983; Igawa S, 1985), improving the detection of small tumours and guiding resections. Given its value in our own patients being staged prior to hepatic resection, it would seem that its use could be extended to the staging of patients with primary colorectal cancer. IOUSS has been shown to be a sensitive method for the detection of colorectal metastases (Charnley RM, 1988; 1989; 1990; 1991; Thomas WM, 1987; Machi J, 1987; 1991; Boldirini G, 1987; Soyer P, 1992; Sugarbaker PH, 1990; Davies AH, 1990; Stewart PJ, 1993). There are, however, little data on the long-term outcome for patients who have been staged by IOUSS (Machi J, 1991). This particularly applies to the rate of appearance of hepatic

metastases not detected by IOUSS at operation and the outcome of patients following the detection of very small metastases by IOUSS. Finally, it may be possible to identify, by IOUSS at the time of their primary colonic surgery, patients who have hepatic metastases suitable for resection.

In the previous chapter, IOUSS has been shown to be comparable to both DBCT and IOE scanning in the detection of known hepatic metastases. This chapter describes a series of patients presenting with primary colorectal cancer in whom IOUSS and IOE scanning have been used to detect the presence of hepatic metastases at the time of potentially curative, primary colorectal surgery. These patients have been followed up by sequential IOE scans to detect and monitor the growth of metastases present at the time of primary surgery and the appearance of metastases occult at the time of operation. In particular, IOUSS and IOE have been evaluated in comparison to palpation at the time of operation.

V.A.1. Aim

This study aims to answer the following questions:

- Can IOUSS be used as part of the routine of laparotomy for patients undergoing resection of primary colonic carcinoma without morbidity?

- Does IOUSS at the time of operation detect more hepatic metastases than visualisation and palpation alone?

- Can IOE scanning at the time of operation be used to confirm the findings of intraoperative ultrasonography?

- Do occult hepatic metastases exist in patients who have been screened by intraoperative ultrasonography at the time of surgery?

- Can repeated IOE scanning be used to detect occult hepatic metastases in the follow up period?

- Can IOE scanning be used to follow the growth of hepatic metastases in patients who are known to have metastases?

- Can repeated IOE scanning be used in the routine follow-up of colorectal cancer patients to improve survival by the early detection of resectable hepatic metastases?

V.A.2. Design

The study was undertaken as a prospective comparison of the three primary methods of investigation: visualisation and palpation by the operating surgeon, IOUSS with visualisation and palpation and IOE scanning.

V.A.3. Patients and method

One hundred and fifty five patients, presenting with a diagnosis of colorectal cancer to two hospitals in the Edinburgh area between 1st of April 1990 and 31st March 1992, were eligible for entry into the study. Eight consultants in the Royal Infirmary of Edinburgh and the Eastern General Hospital, agreed to their patients being followed up within the study protocol. There were 78 males and 77 females with a median age of 70 years (range 37-93 years).

V.A.3.a. Consent and recruitment

Each patient was interviewed prior to surgery and given a written description of the study detailing their involvement. They were then asked to give informed, written consent to each part of the study. Patients having emergency as well as elective operations were included. Since the principle investigator (WFAM) was required to be present at two hospitals, it was not possible to include all potential patients in the study and some were missed as operations were being performed simultaneously at the two separate sites.

The only primary exclusion criteria was that of non consent. Patients were able to withdraw from the study at their own request or at the request of their consultant. In some emergency cases, the intra-operative ultrasound scan was performed at the request of the consultant prior to interviewing the patient. The study protocol, consent forms and information documents were approved by the local hospital ethical committee and the consultants whose patients were included in the study.

V.A.3.b. Protocol

Patients presenting with findings on history, clinical examination, double contrast barium enema or colonoscopy, diagnostic of colorectal cancer, were interviewed. A further full history and examination was undertaken. Patients

consented in writing to all or part of the study and the consultant in charge was informed. IOUSS was performed at the time of laparotomy for resection of the primary colorectal cancer following the technique described in chapter 3. The operative findings and the findings of the intraoperative ultrasonography were recorded on a database proforma (appendix 5). The patients' postoperative course was recorded together with their date of discharge. An IOE scan was undertaken within six weeks of the patients' primary surgery. Patients continued to be followed up in the regular outpatient clinic of the consultant who had performed their operation. Repeat IOE scans were undertaken on a 6 monthly basis for 18 months. When the patients had undergone a total of four IOE scans, they were thanked by letter and discharged from the study (Fig 1.). After each of the IOE scans, a discharge summary giving the results of the scan was sent to the consultant in charge and to the patients' general practitioner. All subsequent management decisions were made by the consultant in charge.

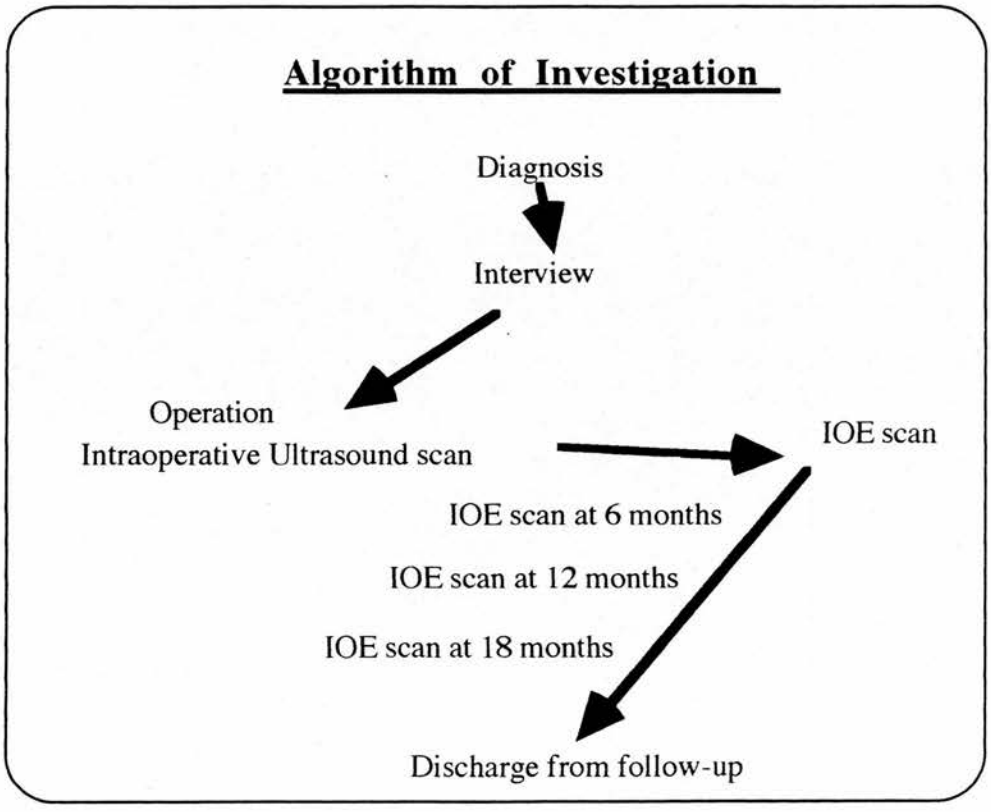

Fig 1. Algorithm of investigation for patients with colorectal cancer within the IOE study protocol.

V.A.3.c. Preoperative investigation

The following investigations were undertaken in the preoperative period: full blood count, serum urea and electrolytes, bilirubin, alanine aminotransferase, alkaline phosphatase, gamma gultamyl transferase, carcinoembryonic antigen, CXR, electrocardiogram, sigmoidoscopy or colonoscopy and biopsy, double contrast barium enema examination and abdominal ultrasonography, where appropriate and as arranged by the patients' consultant.

V.A.3.d. Operative data collection

Each operation was witnessed and recorded by the principle investigator (WFAM). Prior to intra-operative ultrasonography of the liver, the surgeon was asked to examine the liver, both visually and by bimanual palpation, for the presence of metastases. He was then asked to describe the size, position and nature of any masses that he could detect and this information was recorded. Bimanual palpation and intraoperative ultrasonography were then undertaken as a combined procedure by WFAM. This examination was carried out in the manner described previously (chapter III) without extension of the laparotomy wound. Where possible, and within the constraints of their site, lesions detected were biopsied. Biopsy was not undertaken within the trial protocol where it could not be performed without extension of the laparotomy wound, or mobilisation of the liver. The results were recorded and thermal image pictures taken of any lesion seen.

In a small number of patients, the consultant in charge of the operation decided to extend the laparotomy wound or to mobilise the liver in order to obtain biopsies of lesions detected. WFAM assisted in the biopsy of these lesions when requested. In cases where there were a number of metastases of similar appearance, a biopsy was only taken of one lesion and not of every separate metastasis.

Each metastasis found was identified with relation to its segmental anatomy. The position and size of a maximum of 10 metastases were noted, after which only the 10 largest separate lesions were noted. In a number of patients it was not possible to differentiate discreet metastases as large areas of the liver were completely replaced with tumour. All cysts and haemangiomas were similarly documented. In cases where the nature of a cyst was in doubt it was aspirated and the contents subjected to pathological investigation.

V.A.3.e. Post operative data collection

The patients post operative course was recorded with regard to their in-hospital stay, complications and in particular any intra-abdominal collections or infections related to the liver. A repeat serum CEA was also measured on the 10th post operative day. The patients who had intraoperative ultrasonographic examination of the liver and an IOE scan of the liver in the immediate post operative period were offered a further IOE scan every six months for the subsequent 18 months.

Any patient who declined to undergo a follow up IOE scan was requested to undergo a single CT scan in the follow up period. Those who did not have any further scans were followed as far as possible for 18 months after their operation by telephone interview, review of the case notes and through contact with their general practitioner.

V.A.3.f. IOE scanning

The patients were monitored by a senior research nurse (JC) during the period of the IOE infusion and scanning. Pulse, blood pressure and temperature were measured at 15 minute intervals during the infusion and every thirty minutes for the following three hours. At each IOE scan appointment, blood was taken for full blood count, urea and electrolytes, alanine amino transferase, alkaline phosphatase gamma glutamyl transferase, bilirubin, and CEA. The data from each examination was entered into the database .

V.A.3.g. Follow up IOE scanning

All of the patients who were followed up had undergone potentially curative primary surgery. A number of patients were known to have hepatic disease but this did not exclude them from the study. After the initial IOE scan patients were called back to the radiology department at 3 monthly intervals for alternate upper abdominal ultrasonography and IOE scanning (*Fig 2*) noting the size and site of each metastases.

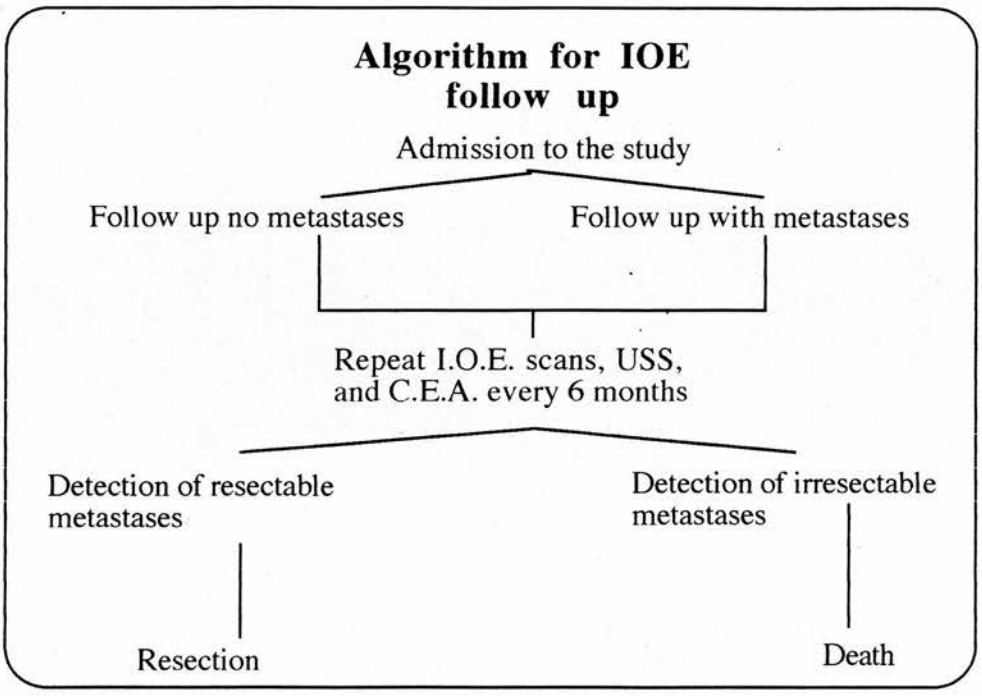

Fig 2 Algorithm for the follow up of patients by IOE scanning and ultrasonography.

Patients were excluded from follow up if they failed to attend for follow up or if they were too unwell to continue in the study.

V.A.3.h. Pathological staging

The colonic tumours, once resected, were sent for pathological assessment and reported using the Dukes staging technique, as described in chapter I

V.A.3.i. Definition of metastases

The size and site of each lesion identified was recorded, for each investigation, onto the database. The presence of a metastasis was confirmed if the lesion was apparent on two independent investigations (palpation, IOUSS, IOE scanning or by positive pathology). During the follow up period the presence of metastases was confirmed by the same criteria, or one of the above plus a rising serum CEA in the absence of local recurrence. In cases where a lesion was identified on the original examination and then "disappeared" on subsequent imaging the evidence was examined critically and a decision made

as to the presence or absence of metastases. This gave an agreed final stage for each patient. Calculation of the accuracy of each investigation has been made in comparison to this agreed final stage.

V.A.3.j. Statistical methods

All of the analysis has been performed using 'Statview SE + Graphics' and dBase III plus programs written by WFAM. Direct comparisons between two groups of discreet variables have been made using the Chi sq test of significance. Where appropriate, non parametric methods of analysis have been used (Mann-Whitney U test or Wilcoxon ranked sign test).

Box and whisker plots have been used to compare groups graphically, with the whiskers at the 10th and 90th percentile and the box containing the first to third quartile, the median being marked by a transection of the box. Bar charts and line graphs have also been used to display data.

V.B. Results

V.B.1. Preoperative data collection

There were 155 patients who presented between April 1990 and March 1992, with a median age of 70 years (range 37 - 93); 79 of these were male. Not all of the patients were submitted to all of the proposed preoperative investigations (Table 1).

Investigation	Number of patients
Chest Xray	140
Pre-op Haematology	155
Pre-op Biochemistry	155
CEA	155
Pre-op Ultrasonography	118
Flexible Sigmoidoscopy	96
Barium Enema	113
Colonoscopy	22
Total number of patients	155

Table 1. Preoperative investigation of 155 patients having laparotomy prior to IOUSS and IOE scanning

Elevation of serum CEA was used to confirm the presence of hepatic metastases. There was only one patient in the series with a single positive IOE scan in whom the preoperative CEA was normal (indicating tumour which did not produce CEA). In this patient (number 14), although, the first postoperative IOE scan was positive, the subsequent three IOE scans were negative. This patient was confirmed not to have metastases on the outcome of repeated IOE scans and not on the CEA level which was an unreliable indicator of disease in this case.

V.B.2. Non consent

Eighty three of 155 patients who had intra-operative ultrasonography performed did not undergo an IOE scan. Their mean age was 72 years (range 37- 93 years), and included 34 men. Of the 83, eight had wide-spread incurable local and hepatic metastatic disease. These patients were considered too unwell by their consultant to be subjected to an IOE scan. Four of these patients died

in the early post operative period. There were a further 34 patients who had widespread disease without hepatic metastases in whom their consultant felt that further investigation would be inappropriate. The remaining 41 patients declined to take part in the study for personal reasons having had the protocol explained verbally and in writing. The primary reasons varied and included a desire that they not be submitted to any further intervention, or spend any more time in hospital. In the case of patients from the Eastern General Hospital, they did not want to go into another hospital (The Royal Infirmary of Edinburgh) for their IOE scan. In 13 patients, the medical staff informed the patients that their cancers had been "cured" and they refused to take part in the study because they felt the detection of metastases could not apply to them. With the consent of the consultants, those of the 83 who survived the first post operative year were offered a single DBCT scan. Only eight patients agreed to this investigation.

The design of the study required patients to be called in for USS of the liver in between IOE scans. This part of the study was discontinued after 48 USS scans had been performed on 38 patients because of lack of resources in the X-ray department and complaints from the patients that they were being called back to the hospital too frequently. There were 7 patients with a positive examination in this small group, 5 of whom had positive IOUSS and IOE scans. Fourteen patients in the group had final confirmation of metastases (*Fig 3, Table 2*).

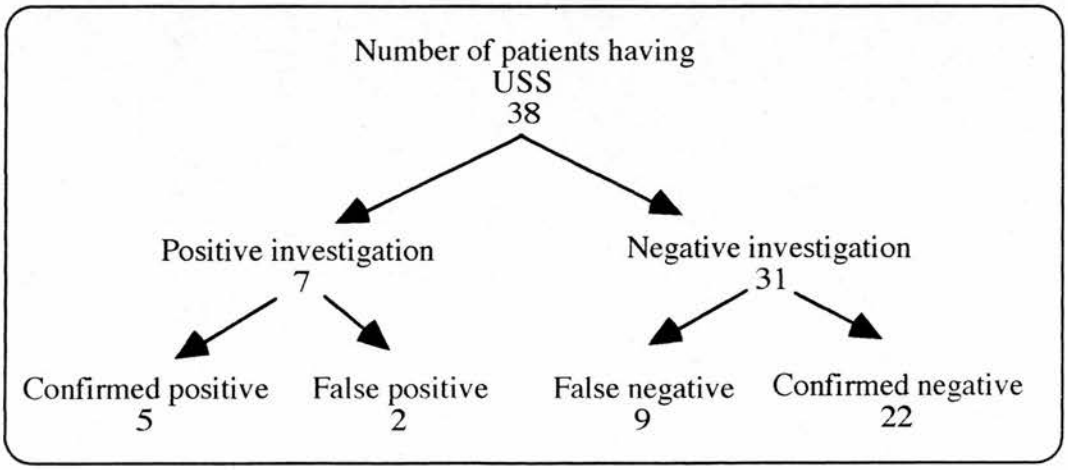

Fig 3. 38 patients who had a USS during the follow up period. The result of the final USS in each patient has been considered for the calculation of statistics.

Parameter	Percentage
Sensitivity	36%
Specificity	92%
Positive predictive value	71%
Negative predictive value	71%
Overall accuracy	71%

Table 2. Accuracy of USS in the detection of metastases in patients during follow up after curative resection of colorectal cancer.

V.B.2.a. Patients within the study

Only those patients who had both an IOE scan and an IOUSS are considered in the remainder of this chapter. A full analysis of all patients who had an IOUSS is undertaken in chapter VI.

V.C. Patients having IOUSS and follow up by multiple IOE scans

Seventy two patients had both an intraoperative ultrasound examination and an IOE scan. On pathological examination of the resected specimen, the primary cancer was found to be of gastric origin in one patient and pancreatic in another. Of the 70 patients remaining to be studied, the median age was 67 years (range 43-88 years) and 46 were men.

V.C.1. IOUSS scanning

IOUSS detected metastases in 16 of the 70 patients whose pathology was confirmed during follow up (*Table 3*)

Patient	M1	M2	M3	M4	M5
7	V	VI			
12	V				
17	II	IV	VIII		
18	VI				
25	VI				
26	II				
57	V				
64	IV	III	II		
82	VI				
89	V	IV	III		
90	VIII	VI			
108	VII				
111	VI				
113	VI				
141	V				
154	IV				

Table 3. Metastases detected by Intra-operative ultrasonography in patients who had evidence of metastases on their subsequent IOE scans. The segments involved are indicated by the roman numerals I-VIII

Three patients who had metastases present on initial intra-operative ultrasound scan but not on the initial IOE scan went on to develop metastases detectable by IOE scanning in the follow up period (patient numbers 12, 111, 113). A fourth, patient 141, had a negative postoperative IOE scan. At operation this patient had a palpable mass in segment V the presence of which was confirmed by IOUSS. The scan also revealed a large number (more than 10) of small metastases spread throughout the liver. The patient, who was well with no evidence of recurrence and with a serum CEA level of < 30u/l at the second IOE scan 12 months after surgery, defaulted from further follow-up within the study. The patient was subsequently admitted and died with hepatic metastases 36 months after surgery.

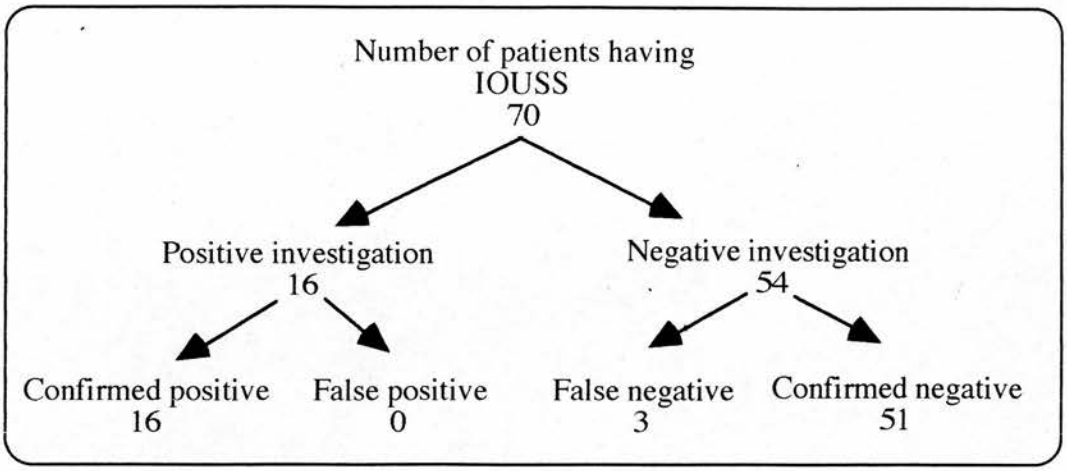

Fig 4 The results of IOUSS in the detection of metastases at the time of operation. There were 3 patients who had no evidence of metastases on their IOUSS who went on to develop metastases in the follow up period. These are false negative investigations for IOUSS.

Of the remaining 56 patients, 3 went on to develop metastases in the follow up period; these patients were false negative results for IOUSS (*Fig 4*). A brief summary of each of these patients is given at the end of the chapter detailing the site and size of the metastases revealed by palpation, intraoperative ultrasonography, IOE scanning and the reasoning behind the agreed final staging. The overall sensitivity and specificity for IOUSS compared to the agreed final stage is detailed in table 4.

Parameter	**Percentage**
Sensitivity	84%
Specificity	100%
Positive predictive value	100%
Negative predictive value	94%
Overall accuracy	96%

Table 4. Accuracy of IOUSS compared to the agreed final stage, in the detection of hepatic metastases for 70 patients who had at least one IOE scan following laparotomy.

V.C.2. IOE scanning

Each patient had a single IOE scan within 6 weeks of the day of surgery and subsequent scans every six months until they had a total of 4 scans or defaulted from the study.

V.C.2.a. IOE Administration

Patients did not display any haemodynamic instability either during the infusion or during the subsequent scanning. The results of these measurements *(Table 5)* show no significant change in any of the vital signs. Thirty percent of patients complained of one or more of the following: metallic taste in the mouth, nausea, "flu" like feeling and mild rigors. Six patients had a more marked reaction to the examination consisting of conjunctivitis, rhinorrhoea and headache. These reactions were all self-limiting and resolved completely within 24 hours of the infusion. There was no evidence of sensitisation in any of the patients receiving multiple IOE infusions and the severity of the adverse reactions of rhinorrhoea etc. did not increase with subsequent infusions.

Two patients had reactions related to the co-administration of Niopam 300 following the infusion of the IOE. The Niopam infusion was not part of the study protocol and was made under the direction of the radiologist performing the IOE scan in an attempt to outline the renal tracts. Both of these patients had moderate angioneurotic oedema of the lips and eyelids associated with rhinorrhoea and headache. This was terminated by the injection of 10 mg of chlorpheniramine BP. Neither of these patients had any evidence of cardiovascular instability. Both were observed overnight and discharged well the following day. These two patients were excluded from further investigation as the exact nature of the reaction was unknown. They were not skin tested for sensitisation.

Parameter	**Mean pre-infusion**	**Mean post-infusion**	**Significance**
Temp °C	36.5	36.6	NS
Pulse $^{Beats}/_{Minute}$	72.4	73.6	NS
BP mm/Hg	132	147	NS

Table 5. Pre and post-infusion of IOE . Temp in degrees centigrade Pulse in beats per minute and BP = mean systolic blood pressure in mm/Hg

There were no exclusions from the trial because of reaction to the IOE emulsion in the patients who followed the trial protocol.

V.C.3. Detection of metastases by IOE scanning at the time of operation

Of the 70 patients, 16 had lesions identified on their initial IOE scan (*Table 6*)

Patient	L1	L2	L3	L4	L5
7	IV	V			
14	V				
16	V	VI	VIII		
17	V	VIII	II	IV	
18	VIII				
25	VII	II	VI	V	VIII
26	II	VIII			
36	IV	V	VIII		
57	V				
64	IV	IV	IV	IV	IV
82	VI	IV			
85	VII	IV			
89	VII				
90	VII	VI			
108	VI				
154	IV	V			

Table 6. Lesions detected by the first postoperative IOE scan. These are identified by a number (L1, L2.....L5) and segment (I, II, ..VIII) .

Lesions had been detected in 12 of these patients by IOUSS (Table 3). In 4 patients (patient numbers 14, 16, 36, 85), the lesions identified by IOE scanning were not confirmed by IOUSS. There was concordance for the number of metastases per patient in 5 cases and concordance of the site of metastases for 8 of 37 possible metastases.

Of the patients who had evidence of metastases on their first postoperative IOE scan and no evidence of metastases on their IOUSS, three went on to have IOE scans in the follow up period (patient numbers 14, 16, 85). None of these showed any evidence of metastases after a minimum of 18 months follow up, confirming these to be false positive investigations. The fourth patient (number 36) who had evidence of cysts on IOUSS, left the study after the first IOE scan and was alive and well with no overt evidence of hepatic metastases at the close

of the study.

Three patients who had a negative IOUSS developed metastases during follow up (patient numbers 3, 99, 106), giving a total of 19 out of 70 patients with metastases by the end of the follow up period.

There were 11 patients in whom the first IOE scan was negative, and one subsequent scan, in the follow up period, was positive without confirmation of metastatic disease. These patients represent false positive investigations for IOE scanning. In patients 80 and 139, the second IOE scan was positive; however the CEA remained normal and so the positive scan result was not confirmed. These two patients had no further scans and remained well at the close of the study. The second IOE scan for patient 35 was positive but the third scan was negative. This patient did not have a fourth scan but was alive and well at the close of the study. Patients 4, 25, 31, 33 had a positive result for the second IOE scan followed by 2 further negative scans. Patient 137 had a positive third scan not supported by any other positive investigation and did not have a fourth scan. Patient 11's third scan was positive and the fourth negative; there was no other evidence of metastases. In patients 24 and 72, the final IOE scan was positive but not supported by any other investigation. All of these scan results are false positive investigations for IOE scanning.

V.C.3.a. Accuracy of IOE scanning

As a number of patients had more than one IOE scan, the total number of scans is greater than the number of patients. In order to gain a true representation of the accuracy of the investigation the analysis is based on the total number of scans performed (*Fig 5*). Some patients have had both positive and negative investigations during their follow up.

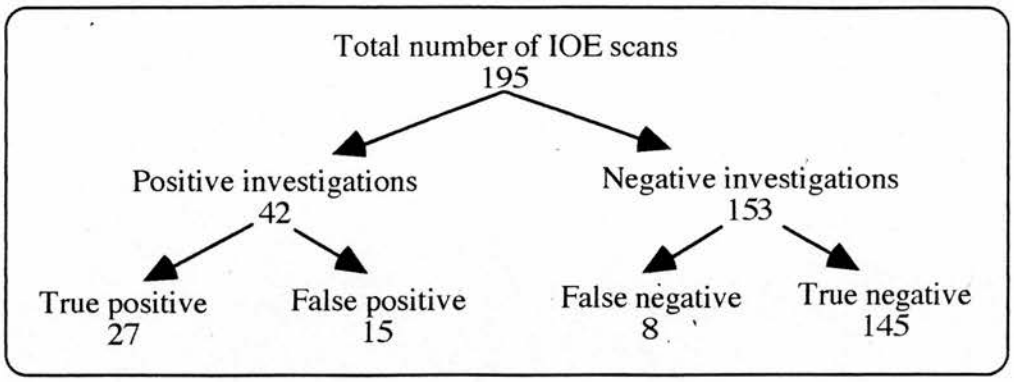

Fig 5. Breakdown of the results of 195 IOE scans performed in the series.

A total of 195 IOE scans have been performed. Of these there were 27 true positive scans, 145 true negative, 15 false positive and 8 false negative. The sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy calculated after 18 months of follow up are displayed in table 7.

Parameter	**Percentage**
Sensitivity	77%
Specificity	91%
Positive predictive value	64%
Negative predictive value	95%
Overall accuracy	88%

Table 7. The accuracy of IOE scanning overall for 195 investigations .

In Table 8, the specificity and accuracy of IOE scanning has been calculated for each of the follow up periods. The subsequent scans were reported in comparison to the earlier scans. However, the level of accuracy of IOE scanning remained constant throughout the series. In three patients, small lesions were detected on IOUSS but not on the first IOE scan. These lesions were all less than 15 mm in diameter and lay in segments V or VI. In each case there was only one metastasis and its presence was confirmed by subsequent IOE scans. There was only one patient (number 36) who had a positive IOE scan within 12 weeks of a negative IOUSS and no subsequent follow up. This

patient had three cysts on IOUSS and the positive IOE scan reported three metastases which were spherical and of uniform density. It is very likely that these 'metastases' were in fact cysts. This patient died before the next IOE scan with advanced local disease.

	Figures expressed as percentages					
Parameter	IOUSS	IOE-1	IOE-2	IOE-3	IOE-4	IOE-All
# of scans	70	70	52	42	31	195
Sensitivity	81	76	82	71	80	77
Specificity	100	93	84	94	92	91
PPV	100	76	56	71	67	64
NPV	93	93	95	94	96	95
Accuracy	94	89	83	91	90	88

Table 8. The accuracy of IOE scanning does not improve with the number of repeat scans .

Patient #	Palpation	Intra-op USS	IOE scan
7	V(60), VI(15)	V(60), VI(15)	IV(40), V(5)
17	II(20), VI1(5), V/VIII(35)	II(20), IV(15), VIII(35)	II(20), IV(15), V/VIII(35)
18	0	VI(14)	VIII(20)
25	II(20), VI(10), VIII(20)	VI(20)	II(10), V(8), VI(10), VII(30), VIII(10)
26	II(10)	II(14)	II(10), II(10)
57	II(10)	V(100)	V(100)
64	IV(100)	II(10), III(10), IV(70)	IV(70), IV(20), IV(10), IV(10), IV(10)
82	0	VI(10) 16 other small mets	IV(8),VI(8)
89	0	III(6), IV(7), V(8)	VII(8)
90	0	VI(35), VIII(40)	VI(20), VII(25)
108	0	VII(20)	VI(20)
154	0	IV(15)	IV(30), V(30)
Patients with metastases on IOUSS and follow up IOE			
12	0	V(12)	VIII(10)
111	VI(15)	VI(15)	II(10), IV(13), IV(4), V(4)
113	0	VI(10)	VI(10), VIII(10)
141	V(12)	V(12) plus more than 10 small metastases throughout the liver.	negative

Table 9. The results of palpation , intra-operative ultrasonography and IOE scanning. Numbers in () represent size of metastases in mm, the affected segment is depicted by roman numerals I.....VIII.

V.C.4. Palpation

At operation, the surgeon felt that he could detect metastases by palpation in 15 patients; the presence of metastases was confirmed in 8 (*Table 9*). The remaining 7 were false positive results for palpation. In 55 patients, the surgeon could not detect any metastases, 44 of these patients had no evidence of metastases at the conclusion of the study. The remaining 11 had the presence of metastases confirmed (*Fig 6 Table 10*).

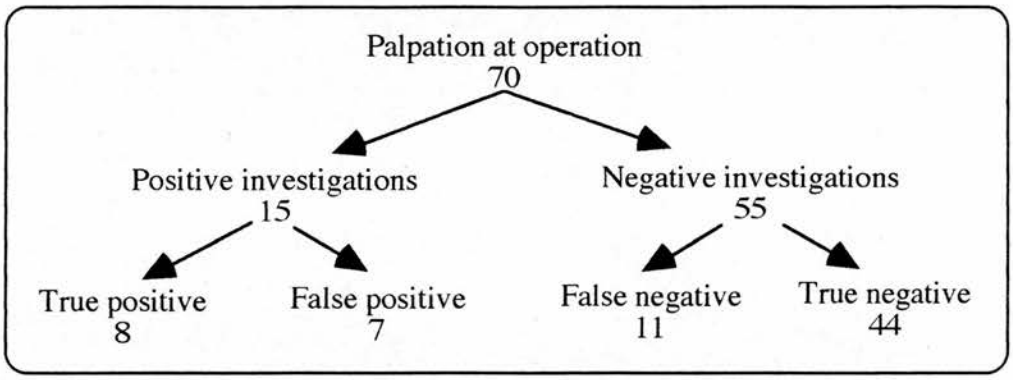

Fig 6 Breakdown of the results of palpation in 70 patients laparotomised for resection of primary colorectal cancer

Parameter	Percentage
Sensitivity	42%
Specificity	86%
Positive predictive value	53%
Negative predictive value	80%
Overall accuracy	74%

Table 10. The overall accuracy of palpation of the liver for hepatic metastases at the time of curative primary resection of colorectal cancer.

Palpation was less accurate than the initial IOE scan (Chi sq = 2.13 1df, $p > 0.1$) and significantly less accurate than IOUSS (Chi sq = 12.67 1df, $p < 0.001$) and overall IOE scan (Chi sq = 7.63 1df, $p < 0.01$) in the determination of the presence or absence of hepatic metastases (Chi sq calculated from a four fold table comparing the total of the true results and the total of the false results for each investigation).

V.C.5. Comparison of number, site and size.

There were 12 patients who had metastases on both their intra-operative ultrasound scan and on their initial IOE scan, and a further 3 who developed positive IOE scans in the follow up after a positive IOUSS at operation. The reported site and the size of metastases showed considerable variation (*Table 9.*).

There were 6 patients with metastases who also had either cysts or haemangiomas identified by intraoperative ultrasonography but not by IOE scanning (*Table 11*).

Patient Number	**Cysts**	**Haemangiomas**
18	0	2
25	6	0
26	0	1
64	1	0
108	2	0
111	2	0
Total	11	3

Table 11. The incidence of cysts and haemangiomas in patients who had hepatic metastases.

These lesions were identified by their appearance on IOUSS alone. The benign nature of these lesions has been confirmed in the follow up period, in particular the presence of multiple cysts. Although cysts can mimic metastases on IOE scanning, their appearance on IOUSS is distinct and quite different from solid metastases. Malignant cysts were present in one patient (number 25); of seven lesions present one was recognised as being malignant as it contained multiple internal septa, debris and a solid component. It is possible that all of the other lesions present in this patient were also malignant cysts in an earlier stage of development.

Haemangiomas were identified by their IOUSS appearance alone and were not confirmed by unenhanced and DBCT scanning.

V.C.5.a. Follow-up IOE scans

Of the 70 patients who underwent an initial IOE scan, 52 returned for a second, 42 for a third and 31 for the final scan.

Sixteen of the 70 patients entered the study having had hepatic metastases demonstrated by IOUSS. Ten of these had 2 scans performed, 5 had three scans and 3 had four scans. IOE scanning was used to monitor the increase in size of the metastases with time, and the appearance of new metastases in these patients.

V.C.5.b. Development of metastases

Three patients developed metastases in the follow up period (numbers 3, 99 and 106). All three IOE scans in the follow up period positive for patient 3. Patient 99 had the third and fourth scans positive. Patient 106 only had one scan in the post operative period and this was positive, CEA estimation at this time was raised at 182 u/l.

V.C.6. Growth of metastases

There were 10 metastases which were monitored over a period of time and from which growth rates could be calculated. There was consistent rapid growth in 5 of the 10 metastases. In 2 there was no growth or very slow growth and in the remaining 3 there was static disease or reduction in size of the metastases. In the patients who showed rapid growth of disease there was no obvious stabilisation of the rate of growth. (*Fig 7*)

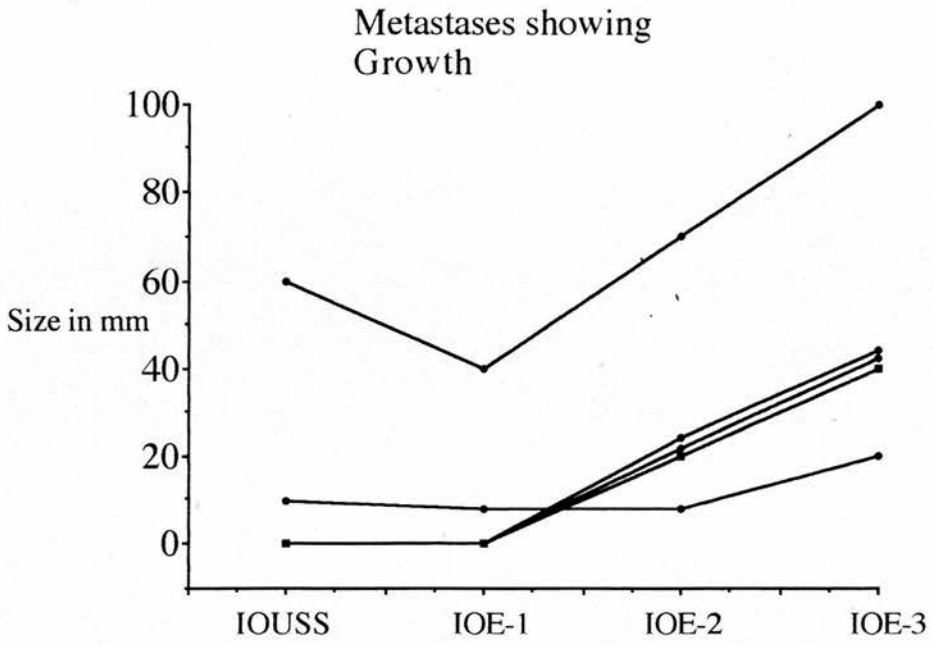

Fig 7. Growth of 5 metastases in patients who displayed growth of metastases associated with decline in clinical condition and death. None of these patients survived to have 4 IOE scans

The rate of growth for the remaining 5 metastases show a mixture of growth and remission with some lesions disappearing altogether. This was an unexpected finding in patients who were not receiving any form of adjuvant therapy. The apparent resolution was complete in 1 patient, the remainder showed either reduction in size or fluctuations with no real increase over the period of follow up (*Fig 8 Plate 1, 2, 3, 4*).

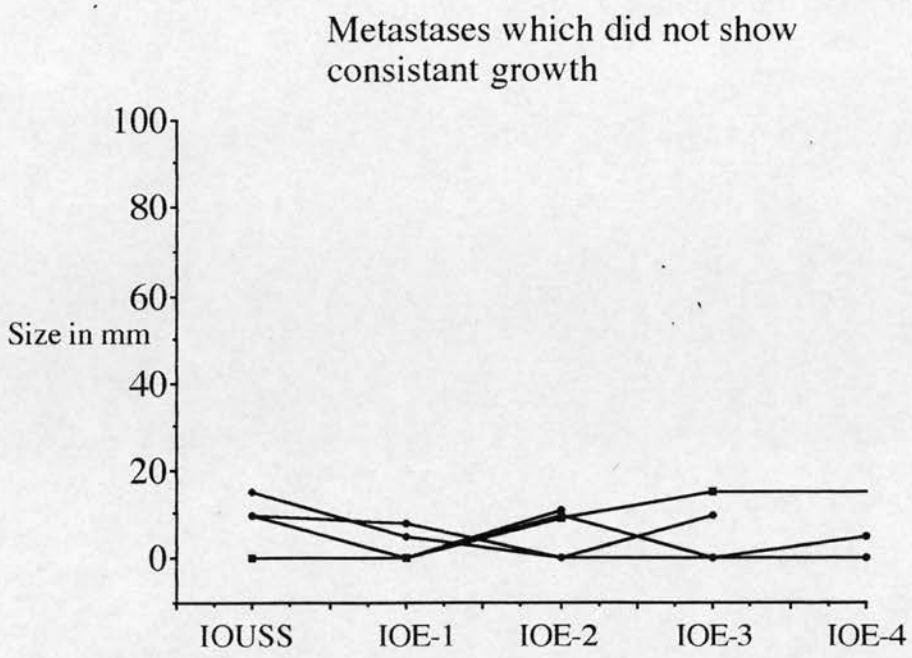

Fig 8. The rate of growth of metastases in some patients slow or static. All of these patient had confirmed metastases on the criteria set out by the study.

Plate 1. Normal IOE scan .

Plate 2 . Six months after plate 1 there is a small area of low uptake in segment VI.

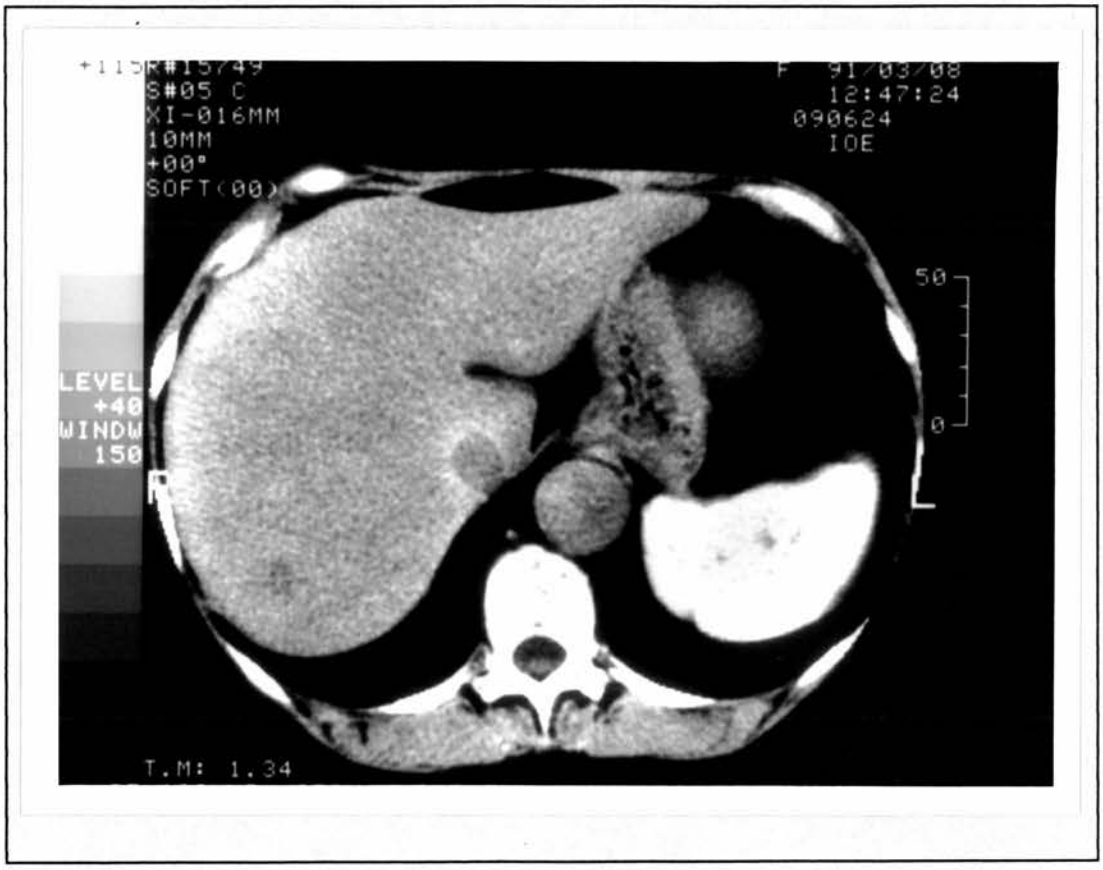

Plate 3 The area of low attenuation is increasing in size.

Plate 4. There is now a clearly defined area of low uptake in segment 6. This was associated with a rise in serum CEA.

V.C.6.a. Resection

Only one patient in this group, with a resectable lesion, was identified. This 46 year old man was found to have a single metastasis in segment V by intraoperative ultrasonography. He received adjuvant chemotherapy with 5 flurouracil and folinic acid in the postoperative period and had two IOE scans and a laparoscopic ultrasound examination which confirmed the presence of the lesion in segment V. Resection of this revealed only nodular hyperplasia with no evidence of residual tumour cells. This patient died with widespread metastatic disease 2 years after his hepatic resection.

V.D. Discussion

IOUSS can be performed at the time of laparotomy for primary colorectal cancer and is a practical method of examining the liver without causing morbidity. The examination adds little to the operation time (5 mins) and has no recurrent cost. The equipment available is robust and easy to use.

IOUSS and palpation

IOUSS at the time of primary colorectal surgery detected significantly more metastases than visualisation and palpation alone. This finding is in concordance with those of others (Machi J,1987;1991; Charnley RM 1991). IOUSS correctly determined the presence or absence of metastases in 67 of 70 patients compared to 52 of 70 for visualisation and palpation. IOUSS was also more accurate than the initial IOE scan: 67 of 70 compared to 59 of 70 (Chi sq = 5.08 1df, $p < 0.05$).

Confirmation by IOE scanning

There were 3 patients in whom immediate post operative IOE scanning failed to detect metastases which were apparent at the time of operation by IOUSS. These metastases appeared on subsequent IOE scans, suggesting that the lesions had increased in size or that IOE scan reporting was more accurate when a number of previous scans could be compared to the current scan. As the criteria for scan reporting included a number of comparative statements (to previous scans) it was expected that the accuracy of the scan reports would increase with the number of scans undertaken, this was not the case. The accuracy rate remained between 83% and 91% throughout the series. Repeated IOE scanning in the follow-up period can be used to confirm the results of IOUSS and in this series eventually detected all of the lesions seen by IOUSS at operation. There was no significant difference in the accuracy of IOUSS and the overall accuracy of IOE scanning in the 70 patients (Chi sq 3.28 1df, $p > 0.05$)

V.D.1. Minimum size for detection by IOUSS

There were lesions present at the time of operation which were not detected by IOUSS. This may have been either because of an error in performing the scan, or because the lesion was not detectable by virtue of its echogenicity or its size or both of these factors. The exact minimum size for detection of a metastases

is unclear. One very small lesion (4mm) was detected and proven by biopsy. Previous studies using cadaveric material (Charnley 1988) have shown that 2 mm highly echogenic foci, created by injection of gelatine into the hepatic vasculature, could be detected by a 7.5 MHz probe. Lesions smaller than this were not detected. IOUSS scanning detected all lesions which were subsequently detected on the first IOE scan and a number which appeared on later scans, suggesting that IOUSS could detect metastases at a smaller size than IOE scanning. There was considerable inconsistency between the size of lesions reported by both investigations (Table 9). This may account for some of the smaller lesions being undetected by IOE.

Repeat IOE scanning in follow-up

Technically, repeated IOE scanning can be used in the follow-up of patients with colorectal cancer. Patients do not become sensitised to repeated infusions of the contrast agent and the enhancement is maintained in subsequent scans. There is no evidence of accumulation of IOE in the livers of the subjects following repeated scanning at 6 monthly intervals and there is no evidence of any other longer term ill effects of the technique within the study period.

It was however very difficult to recruit patients into this type of follow up and the refusal rate was high. The principle factors were; a genuine wish to escape the clinical environment of the hospital, denial of the possibility that the cancer might return (sometimes fuelled by the attendant medical staff), a wish to avoid further injections, the side effects of the IOE infusion and finally within the trial patients from the EGH did not wish to come to the RIE for the IOE scan. Although the reporting of side effects was low it is possible some of the 56% of patients who defaulted over the 18 months of the trial did so because of side effects which they failed to report.

Benign lesions on IOE scan

IOE scanning may not readily detect the differences between cysts and small metastases. The incorrect diagnosis of cysts as metastases increased the false positive rate for IOE scanning in the detection of metastases. The presence of a cyst may be inferred by the lesion having a perfectly smooth outline and an amorphous centre, however as the lesions become smaller so it becomes more difficult to make this distinction. It was not possible to differentiate small cysts from metastases by IOE scanning. There is no published data describing the detection of cysts by IOE scanning. For the same reasons haemangiomas

cannot be differentiated from metastases by IOE scanning. They can however be demonstrated by bolus injection of contrast during normal CT scanning. A problem remains how to select patients to have both IOE scanning and DBCT scanning as there may be no indication from the IOE scan that the lesion in question is in fact a haemangioma. DBCT scanning may not be performed at the same time as IOE scanning. When this was performed outside the study protocol in two patients they both suffered reactions which required hospital admission and treatment. The accurate detection of both cysts and haemangiomas is an advantage of IOUSS over IOE scanning.

Growth of metastases

IOE scanning was used to monitor the growth of metastases in patients with time. This has identified two groups of patients: those who have rapidly expanding lesions, which behave as expected, and those in whom the metastases are more indolent. In patients displaying growth, IOE scanning was able to detect the same metastases on sequential scans and comparisons of size could be made. This only occurred for 5 individual metastases in the entire series. In a further 5 metastases, there was sporadic growth and resolution leading to fluctuation, rather than a steady increase in size. There are a number of possible explanations for this: the apparent metastases which did not grow were not in fact metastases but some other lesions or that some tumours were very slow growing where others were very aggressive, or the suppression of growth was brought about by the repeated infusion of IOE. Each of the 3 patients with indolent growth had other factors to suggest that the lesions in question were metastases.

Growth rates for metastases can very greatly (Finlay IG, 1988). Finlay gives no detail of the type of enhancement used and the tabulated data had been subjected to a complex conversion to attempt to estimate the volume of the tumours assuming that they were ellipsoid and not spherical. Unfortunately this makes it very difficult to calculate the diameter of the metastases, although the smallest had a total cell number of 3.8×10^8. A previous paper from the same author (Finlay IG, 1983) gave the number of cells / gram of tissue as 1×10^9. Assuming the same conversion factor, this would give a mass of 380 mg or a volume of 380 mm^3 assuming a tissue density of approximately 1 gram / cm^3. A spherical metastases of this volume would have a diameter of approximately 9 mm. The author has stated that metastases smaller that 1.5 cm

diameter appeared to be ellipsoid on the scans. Lesions of 1-1.5 cm diameter are at the limit of resolution for a scanner of the type used in this study. The columnation used was 13 mm; i.e. the scanner compiled information on the radio density of tissues from a slice 13 mm thick, at 1.5 cm intervals. Using this type of setting, small lesions only take up part of the thickness of the scan. The area of low attenuation is a composite of information from different areas of the metastasis. In particular the apparent diameter of the same metastases may vary considerably depending on where in the plane of scan happens to fall in relation to its equator. There is little to support the hypothesis that, when less than 1cm in diameter, metastases are ellipsoids which become spherical when they reach a diameter of 1.5cm. In papers which have reprints of actual scans, there is no evidence to show that small lesions are ellipsoids (Alderson PO, 1983; Adson MA, 1984; Rifkin MD,1987; Brower ST,1989; Goulet RJ, 1990; Ravikumar TS, 1987; Olsen AK, 1990; Castaing D, 1986; Parker GA, 1989; Bismuth H,1987; Boldrini G,1987; Clarke MP, 1989) Pathological evidence from resected specimens in the series of patients reported in chapter 4 have shown small metastases to be spherical or near spherical the appearance of apparent ellipsoid lesions is likely to represent artefact. This study has reported the diameter of small lesions on CT and IOE scans using 10 mm columnation at 10 mm intervals to scan the entire liver and with breath holding to eliminate respiratory movement. The diameter of lesions seen on IOE scanning is an inevitable approximation which becomes more accurate as the lesion increases in size. For this reason accurate measurement of metastases is not possible using these settings when the maximum diameter is approaching 1 cm.

V.D.1.a. Partial volume effect

Partial volume effect occurs when the diameter of the metastases is smaller than the columnation width of the CT scan. As the size of the metastasis approaches the beam columnation width, only part of the beam crosses the maximum diameter of the metastasis. The remainder of the beam passes through a section of the metastasis of smaller diameter or misses the metastasis altogether. This causes blurring of the margin of the metastasis on the scan (Fig 9). The partial volume effect can be compensated for to some degree by altering the gate setting of the CT scanner. Gating allows the range of grey from black to white seen on the CT image to be adjusted to correspond to a particular level of X-ray signal attenuation. This has an effect similar to adjusting the contrast on a TV picture. However, measurement of lesions which approach the columnation width of the scanner includes a substantial error.

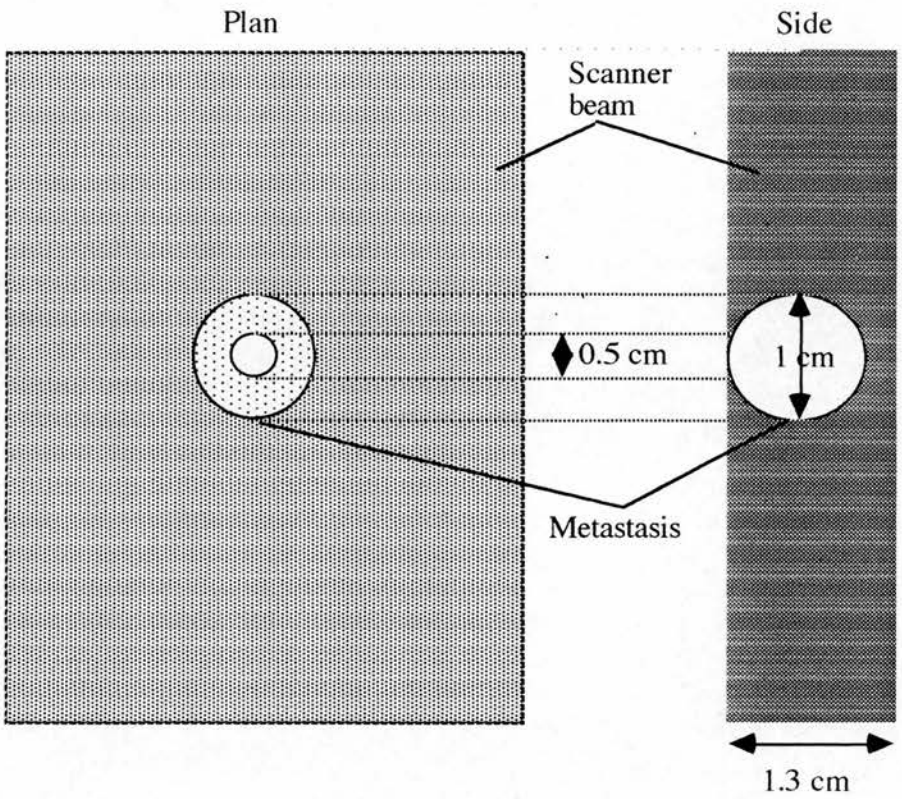

Fig 9. As the size of a metastases approaches the columnation setting of the CT scanner it becomes more difficult to accurately measure its diameter.

Patients in our series who had large (greater than 1.5 cm) metastases all displayed growth. The small metastases in patient 113 appeared to decrease in size and one metastasis disappeared altogether. These were at the lower limit of resolution for IOE scanning. It is likely that the apparent disappearance of a lesion and its subsequent reappearance represents a failure of detection rather than a biological event. Patient 82 was found to have 14 small (about 1 cm) metastases on palpation and IOUSS; not all of these were detected by IOE scanning because they were too small. Furthermore, if there is little or no normal liver present the technique will fail as IOE uptake only occurs in normal liver parenchyma. Liver function tests are unfortunately a poor indicator of the degree of liver replacement and may be normal in patients with more than 80% replacement (McGarrity TJ, 1987).

IOE scanning reduces the partial volume effect to some degree. The greater the contrast between areas of normal liver and the metastases, the clearer the margins. However, the measurement of diameter of lesions approaching the

limit of resolution of the technique will include an unavoidable random error. This error is magnified by attempting to calculate volumes from the scans.

V.D.1.b. Resectable disease.

From these data it is apparent that the growth of some metastases can be detected and followed by the use of repeated IOE scanning. In chapter III, IOE scanning was shown to be more accurate in the detection of metastases than DBCT and is the investigation of choice. At the time of operation, IOUSS with palpation was marginally more accurate in the detection of metastases than IOE scanning, but failed to detect very small and microscopic metastases that were present. These occult metastases missed by IOUSS were detected in the follow up period by IOE scanning. In this series these small metastases have continued to appear throughout the follow up period. Published data shows that 80 % of hepatic metastases will be apparent within the first 24 months of surgery (Finlay IG, 1983; Machi J, 1991).

There was no evidence to suggest that scanning in the postoperative period identified patients with more aggressive disease, although in this series the appearance of hepatic metastases heralded a rapid decline in clinical condition in some patients and was associated with rapid and continued growth of the metastases until death. Others patients were in a more stable state in terms of growth and survived to the end of the study. This would suggest that patients with slowly progressive disease might have a survival advantage. Slow growth of the metastases will also increase the lag time from operation to the detection of occult metastases (by routine clinical follow-up) in the general population of patients following colorectal surgery. Might such a delay indicate a better prognosis? Review of the data in chapter III suggests not and reveals that the duration of lag time (the time between primary resection of a colorectal cancer and the appearance of a metastasis, detected by either abdominal ultrasound or DBCT scanning) was not related to the presence of resectable disease or therefore prognosis.

The series of patients having repeated IOE scans is small and there were only 2 patients who had resection of their metastases (3%); less than other series (Coppa GF, 1985; Sugarbaker PH, 1976). There are no published data relating to the detection rate of hepatic metastases in Scotland or the rate of referral for resection. It would appear from the crude data (the number of patients presenting with colorectal cancer per annum in Scotland is 2700) and the results given in chapter IV, that 81 patients per annum should have

resectable hepatic metastases, 24 of whom (30%) would expect to have survive for 5 years if resected. We detected only two patients within the first 2 years of follow-up, both of whom died with recurrent disease following hepatic resection. It is possible that other patients in the series may develop resectable metastases in the future and undergo successful resection.

In order to select patients who would be suitable for hepatic resection, it is necessary to have 2 IOE scans with a period of 3 months inbetween. Rapid growth of the metastasis or appearance of more metastases during this time would prejudice against resection. Patients who display slow growing or static disease are more likely to undergo resection. Their improved survival after resection may be a reflection of the more indolent nature of their disease. To select patients in this manner reduces the number who undergo a technically successful resection only to succumb to recurrent disease in the following 5 years. Without a prospective trial it is not possible to say if it is the resection or the selection which improves survival. Historical data, however, supports the view that patients with hepatic metastases who do not undergo resection have a negligible 5 year survival (Wagner JS, 1984; Cady B,1970; Arnaud JP, 1984; Bengmark S,1969; Scheele J,1991)

Computer enhanced tomography has become the mainstay investigation in the detection and accurate delineation of hepatic tumours in the past decade. Advances in the technology of image capture and in the processing power of computers has improved the quality of the images available for reporting. The need for even greater resolution in hepatic imaging, to detect the small metastases from colorectal cancers has led to the development of contrast agents that improve the detection of intrahepatic malignancy. IOE scanning is one of the few successful techniques that has been developed to enhance hepatic CT scans looking for hepatic malignancy. Its major advantages are its ease of preparation, administration, the quality of the images obtained and its repeatability. This is weighed against the limited side-effects and its cost. Although 30 % of our patients had some form of mild reaction to the scan it did not cause distress nor were side effects cited as a reason for refusing further scans in the follow up period.

At the time of surgery patients response to invitation to further investigations was dependent to a large degree on the information they had been given and their perception of their disease. Patients who knew and understood that they had a malignant disease which could spread, generally agreed to the study on the grounds that early detection of recurrent disease would be to their benefit.

In particular patients in whom IOUSS and palpation had suggested metastases, and who were not too unwell to undergo further investigation, agreed to the study. Those who did not agree were generally patients who had been told that their "blockage" had been removed. Some patients did not know that they had had a cancer and others had been informed that they had been cured. These patients could not be consented because it was impossible to discuss their subsequent investigation, which was designed to detect residual, occult disease, when they had never been accurately informed of the exact nature of their primary disease.

This series was unable to show that repeat IOE scanning could be used in the routine follow up of all patients following resection for colorectal cancer as patients would not tolerate this form of follow-up. Less than half of the patients who were eligible actually consented to the study.

IOUSS is the gold standard investigation for the detection of hepatic metastases at operation and matches the accuracy of the IOE scanning, the most accurate preoperative investigation. IOUSS precludes the need for pre-operative investigation of the liver in patients who require a laparotomy for relief of their primary symptoms. A small number of patients (4%) have metastases which are not detected by IOUSS at the time of operation, these may be detected by IOE scanning, within 18 months of operation, as they grow. In this series patients who had hepatic resection of metastases detected by IOUSS / IOE scanning did not gain any survival benefit.

Chapter VI

IOUSS at the time of primary resection for colorectal cancer.

VI.A. Introduction

The previous chapter has shown that, in a select group, IOUSS is more accurate than IOE scanning for the detection of hepatic metastases at the time of primary resection of colorectal cancer. IOUSS in particular is specific and of high positive predictive value. This information has been used to review the presentation and operative details of 155 patients who had an IOUSS performed at the time of primary resection for colorectal cancer. As IOUSS has been shown to have a PPV of 100% and an accuracy of 94%, the results of IOUSS in this group of patients are considered to be true without supportive data.

VI.A.1. Aim

To use IOUSS to stage accurately a group of 155 patients who had colonic resection for suspected malignancy and to answer the following questions.

- Is IOUSS more accurate than simple palpation at the time of operation?

- Can IOUSS alone be used to improve peroperative staging?

- Does pathological staging of the resected specimen reflect accurately the stage of disease present in the patient ?

- Could improved staging alter management decisions, and, in particular, identify patients with resectable hepatic metastases?

VI.A.2. Patients and methods

The patient group has been described (Chapter V) and includes all 155 patients who had an IOUSS performed at the time of their primary surgery. The

method used to perform the examination is described in chapter III. Patients who were followed up by IOE scanning have been described previously. Details of disease stage and preoperative symptoms and signs were collected at the time of operation. All of these patients have been followed up via either their GP or their hospital consultant. The statistical analysis and graphics used have been described in previous chapters.

VI.A.2.a. Primary diagnosis

Of the 155 patients with a preoperative diagnosis of colorectal cancer, a number of patients were found, at operation, or on subsequent examination of the resected specimen, to have another primary pathology (*Table 1*) .

Pathological diagnosis	Number of patients
Colorectal cancer	147
Diverticular disease	4
Gastric cancer	3
Pancreatic cancer	1

Table 1. The pathological diagnosis in patients undergoing laparotomy for suspected colonic carcinoma who had an IOUSS

Patients who did not have colorectal cancer have been excluded, leaving 147 patients in the study group

VI.B. Results

VI.B.1. Pre operative staging

Although 90% of patients had a preoperative chest Xray, only 76% had a preoperative ultrasonography (USS) of the liver. Visualisation of the colon by barium enema was undertaken in 72% of patients while 61% underwent flexible sigmoidoscopy. Complete colonoscopy was performed in 14%. Only 65 patients had a pathological diagnosis before their operation. This led to 8 (5%) patients having an IOUSS who did not in fact have colorectal cancer. One patient with gastric cancer and the patient with pancreatic cancer had hepatic metastases.

VI.B.2. Pre operative ultrasonography

USS was performed in 119 patients who had colorectal cancer. Eight patients had a positive investigation which was confirmed by IOUSS, 111 patients had a negative examination, which was confirmed by IOUSS and by follow-up in 76 and there were 35 false negative examinations and no false positive examinations. In those patients who had metastases detected by both USS and IOUSS, USS detected 12 (41%) of the 29 metastases present (*Fig 1. Table 2.*).

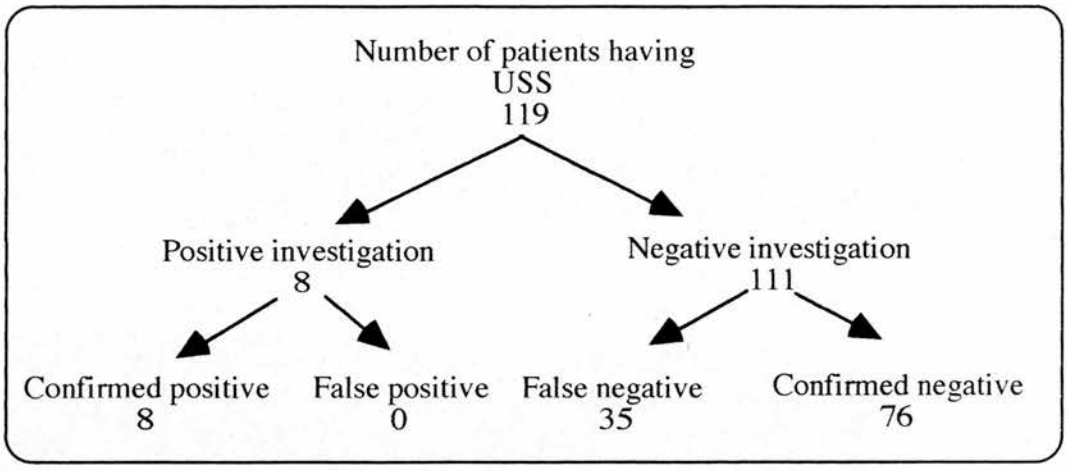

Fig 1. The results for pre-operative USS in the detection of patients with hepatic metastases from colorectal cancer.

Parameter	Percentage
Sensitivity	19%
Specificity	100%
Positive predictive value	100%
Negative predictive value	68%
Overall accuracy	71%

Table 2. The accuracy of pre-operative ultrasonography in the detection of patients with hepatic metastases from colorectal cancer.

VI.B.3. Intra-operative ultrasonography

One hundred and forty seven patients with colorectal cancer had intraoperative ultrasonography performed. There were no complications involved with the investigation and there was no associated morbidity. The scan was incomplete and confidence in its findings were low in only 11 patients. The most common problem was access to the liver being limited by adhesions from previous surgery.(*Table 3*).

Limiting Factor	Number of patients
Adhesions to the liver	9
Adhesions and peritonitis	1
Abnormal hepatic anatomy	1
Total	11

Table 3. Eleven patients had an incomplete scan of their liver . The abnormal hepatic anatomy was a complete congenital absence of segments II, III, IV and abnormal position of segment I. This prevented confident assessment of the presence of metastases.

In two of the 9 patients who had adhesions, access was also limited because the primary colonic resection was performed through a small transverse incision in the lower abdomen.

VI.B.3.a. Morbidity

There was no damage caused to the liver by the ultrasound probe or the surgeons hand in palpating the liver. Neither " Tru-Cut" biopsy nor FNA was associated with any evidence of bleeding or bile leakage. There were no sub diaphragmatic or sub hepatic infection related to the manipulation of the liver during the scanning procedure.

VI.B.3.b. Biopsy

Biopsy was undertaken in 9 patients. The presence of malignancy was correctly identified in 6 of 9 patients with metastases and in the remaining 3, the pathology result failed to confirm the presence of clinically apparent metastases. All 3 of these patients developed gross metastatic disease or died with hepatic metastases in the follow up period. Biopsy was often difficult to perform through the low transverse incisions favoured by some of the

surgeons. With a positive predictive value of only 67%, biopsy was not a satisfactory standard against which to judge IOUSS.

VI.B.3.c. Equipment failures

There were three equipment failures in the 24 months, and all of which were related to the handling of the probes during cleaning and connection. In the first one of the scanning heads was dropped onto a hard floor. In subsequent use one of the crystals in the probe head failed, giving a loss of a portion of the scan. This fault could not be repaired and the probe had to be replaced.

In the second instance, the multi connector/sender unit of the probe was accidentally immersed in 'Cydex' during the sterilisation process. The fault was recognised when the probe was connected to the echo camera. The probe was taken directly to the supplier, repaired the same day, and was returned to operation, without further fault, the following day.

The third failure was related to the design of the multi-pin connector in the connector / sender unit. A member of staff attempted to connect the unit by forcing the multi-pin connector into the base unit while it was not correctly aligned within the socket. This bent one of the pins in the connector so that it failed to make contact. The fault was recognised on inspection of the unit and corrected by gently realigning the connector pin to its original position. All three failures were related to poor treatment of the equipment. There were no further faults related to the ultrasonographic equipment.

VI.B.3.d. Palpation results

Palpation revealed possible metastases in 38 of the 147 patients and their presence was confirmed by IOUSS in 27 patients. Of the remaining 109 patients, 16 had metastases confirmed by IOUSS or follow up IOE and 93 had no evidence of metastases at the end of the study (*Fig 2. Table 4.*).

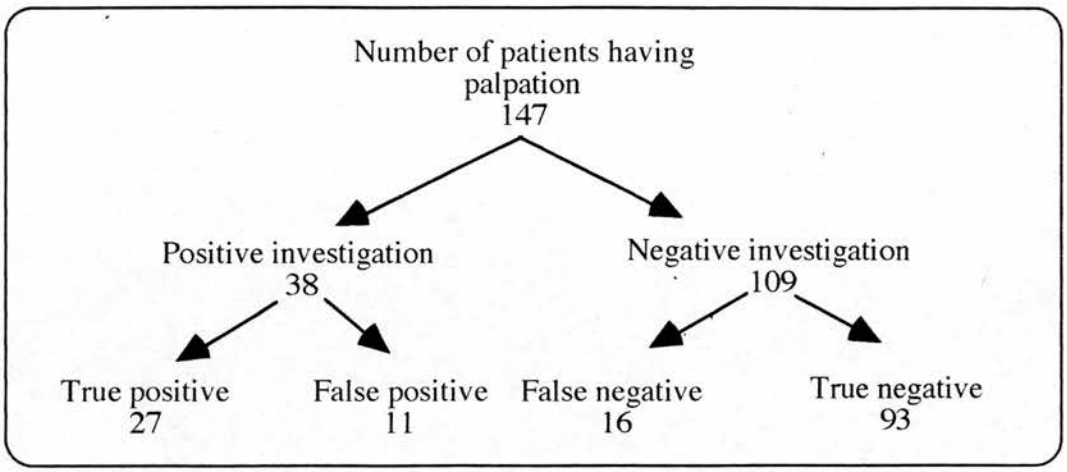

Fig 2 The results of palpation at laparotomy in the detection of hepatic metastases.

Parameter	Percentage
Sensitivity	63%
Specificity	89%
Positive predictive value	71%
Negative predictive value	85%
Overall accuracy	82%

Table 4 Accuracy of palpation at the time of operation compared to the final agreed stage in 147 patients.

Palpation detected less of the patients with metastases than IOUSS (Chi sq = 11.42 1df $p < 0.001$)

VI.B.3.e. Scanning results

Lesions detected by intraoperative ultrasonography		
Lesion	Number of lesions	Number of patients
Hepatic metastases from colorectal cancer	120	40
Hepatic cysts	47	24
Haemangiomata	4	3
Cysts on the Right Kidney	3	3

Table 5. A number of pathologies other than hepatic metastases were detected by intraoperative ultrasonography.

Intraoperative ultrasonography revealed a number of pathologies (*Table 5*).

Thirty-eight patients had lesions which, detected by palpation and / or inspection of the liver were taken to be metastases by the surgeon at the time of operation. In 27 of these patients, the diagnosis was confirmed by IOUSS whilst in the remaining 11 patients, the scan demonstrated cysts which corresponded to the palpable lesions. A further 13 patients had impalpable hepatic metastases which were detected by IOUSS alone giving a total of 40 (27%) of the 147 patients with a diagnosis of colorectal cancer with metastases detectable at the time of operation (*Fig 3. Table 6.*). In one patient, the scan and palpation revealed what appeared to be a metastases in the left lobe of the liver. This was resected by the surgeon at the time of primary colonic resection. Pathology revealed the lesion to be a cavernous haemangioma and not a metastases. This was the only false positive investigations for IOUSS in the series.

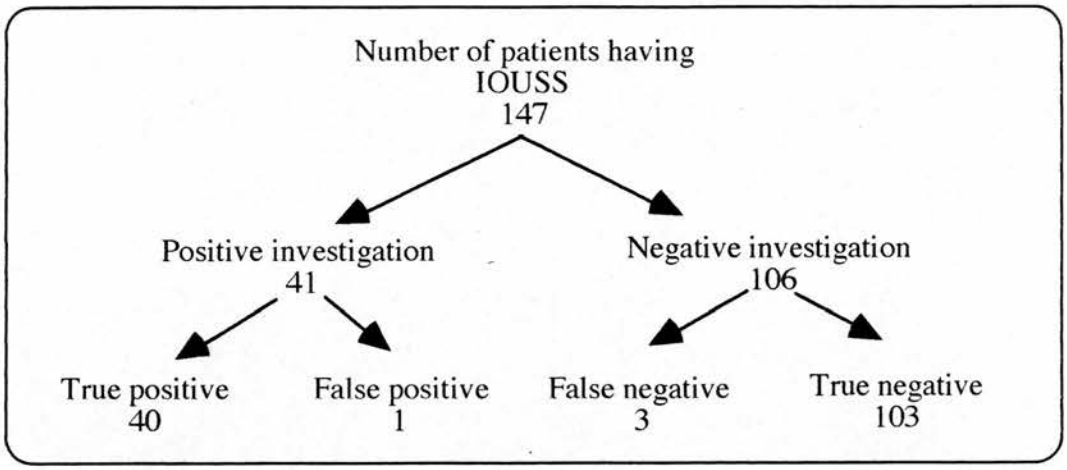

Fig 3 . The results of IOUSS in 147 patients undergoing curative resection for colorectal cancer.

Parameter	Percentage
Sensitivity	93%
Specificity	99%
Positive predictive value	98%
Negative predictive value	97%
Overall accuracy	97%

Table 6. The accuracy of IOUSS in the determination of the presence of hepatic metastases in patients with colorectal cancer.

Both the hepatic cysts and the renal cysts were easily identified by intraoperative ultrasonography. The haemangiomas were identified by their distinct

echogenicity within the lesion and posterior acoustic shadowing.

VI.B.3.g. Hepatic anatomy

In all but one patient the internal hepatic anatomy of the portal pedicles conformed to the recognised pattern . The major hepatic veins were present as were the portal structures with recognisable primary and secondary confluences. In the one case, previously described, the left portal pedicle was absent and the entire - small - left lobe was supplied from the right anterior portal pedicle. The caudate lobe was supplied by small branches from the porta hepatis and drained directly into the vena cava.

VI.B.3.h. Metastases.

The smallest colorectal metastasis detected was 4 mm in diameter lying in segment VI anterior to the right kidney (*Plate 1*). The most common appearance was of a "bulls eye" lesion (*Plate 2*). These metastases were usually

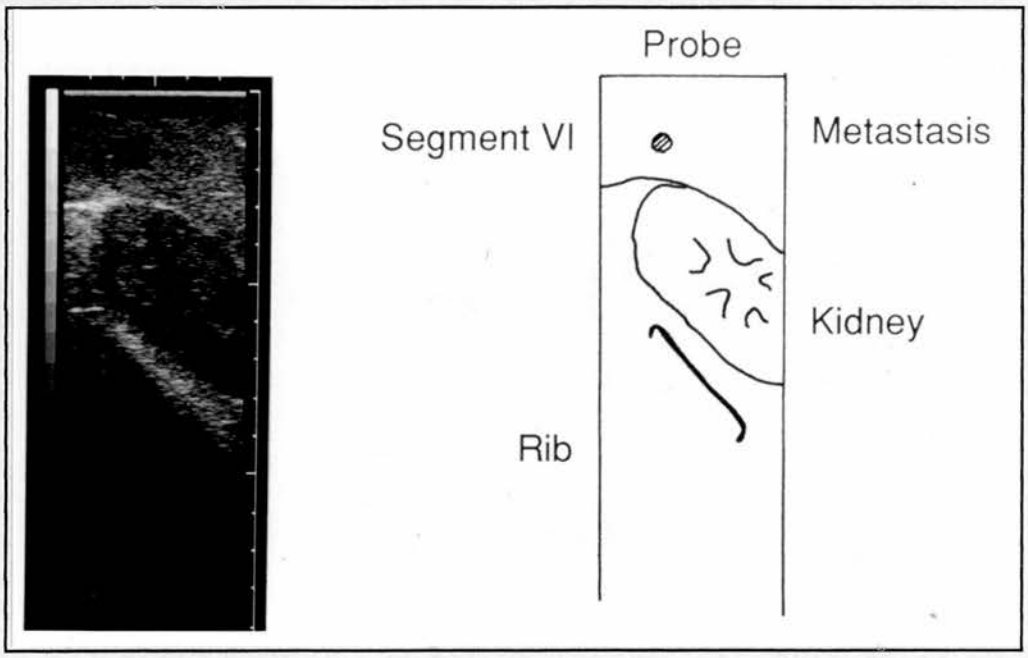

Plate 1 small metastasis anterior to right kidney.

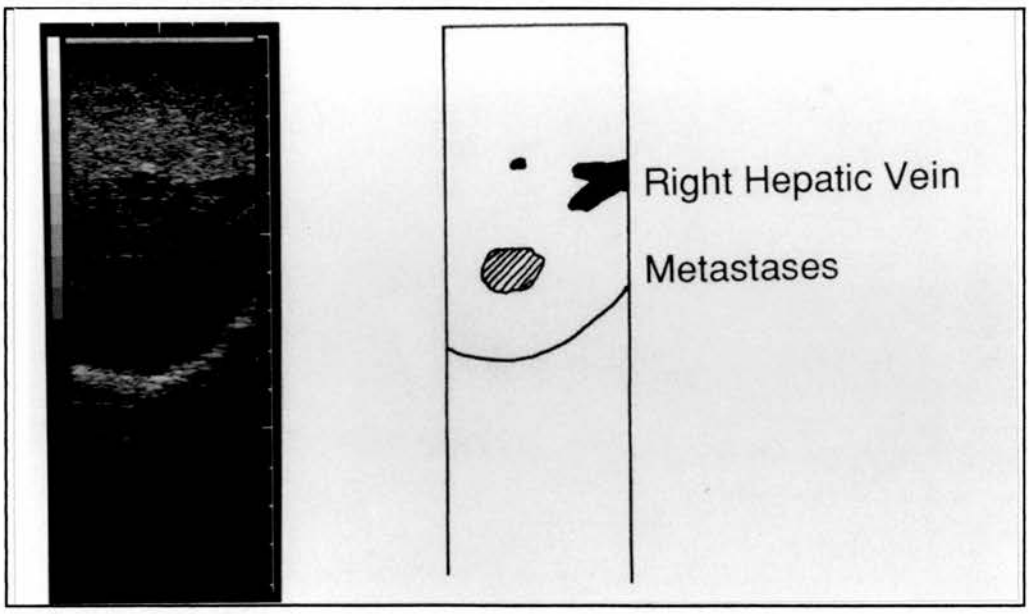

Plate 2 Bulls eye metastasis

easy to identify. The largest metastasis detected was more than 10 cm in diameter. In one patient, a large iso-echoic conglomeration of several metastases was only identified because of its derangement of the intrahepatic anatomy. The tumour deposit could be seen and palpated but could not be differentiated from normal liver by its echogenic profile, but only by its mass effect.

VI.B.3.i. Metastases related to stage

The Dukes stage was recorded by the pathologist in 120 patients. These were: Dukes A in 10, Dukes B in 51, Dukes C1 in 46, Dukes C2 in 12 and Dukes D in 1(resected local invasion of the anterior abdominal wall). A number of these patients had metastases (*Table 6*). The incidence of metastases increased with the stage, patients with stage C2 disease having 1.7 times greater risk of metastases than patients with Dukes A disease.

Dukes stage	Number of patients	Number with metastases (%)	Total number of metastases	Average met' per patient
A	10	3 (30%)	5	1.6
B	51	9 (18%)	22	2.4
C1	46	10 (22%)	29	2.9
C2	12	6 (50%)	22	3.6
D	1	1 (100%)	4	4
Total	120	29 (24%)	82	2.8

Table 6 The number of metastases detected per patient increases with more advanced Dukes stage.

This difference does not reach statistical significance using the Chi Sq. test for any single Dukes stage when compared against the rest of the series. Using the results of IOUSS to reassign patients stage corrected for the presence of distant (hepatic) metastases there were: 7 Dukes A, 42 Dukes B, 36 Dukes C1, 6 Dukes C2, and 29 Dukes D.

VI.B.4. Other factors related to metastases.

VI.B.4.a. Pre operative weight loss

There were 69 patients who complained of weight loss in the preoperative period, 20 of whom had hepatic metastases at operation and 49 of whom did not. Of the remaining 86 patients, 18 had metastases and 68 did not. Using a two by two contingency table with one degree of freedom, patients with weight loss were not significantly more likely to have metastases than those who did not (Chi sq = 0.67 1df $p > 0.10$).

VI.B.4.b. Abdominal pain

Out of all 147 patients, when asked, 82 said that they had abdominal pain, of these 27 had metastases at operation. The remaining 65 patients did not complain of abdominal pain, 11 had metastases and 54 did not. Significantly more patients who had abdominal pain had metastases than those who did not (Chi sq = 4.84, 1df. $p < 0.05$).

VI.B.4.c. . Duration of symptoms

The duration of symptoms endured by patients prior to surgery varied greatly. In this series some patients had a history of more than 13 years. Patients who had a longer period from their first symptom to diagnosis tended to have fewer metastases than those with a short period (*Fig 4.*).

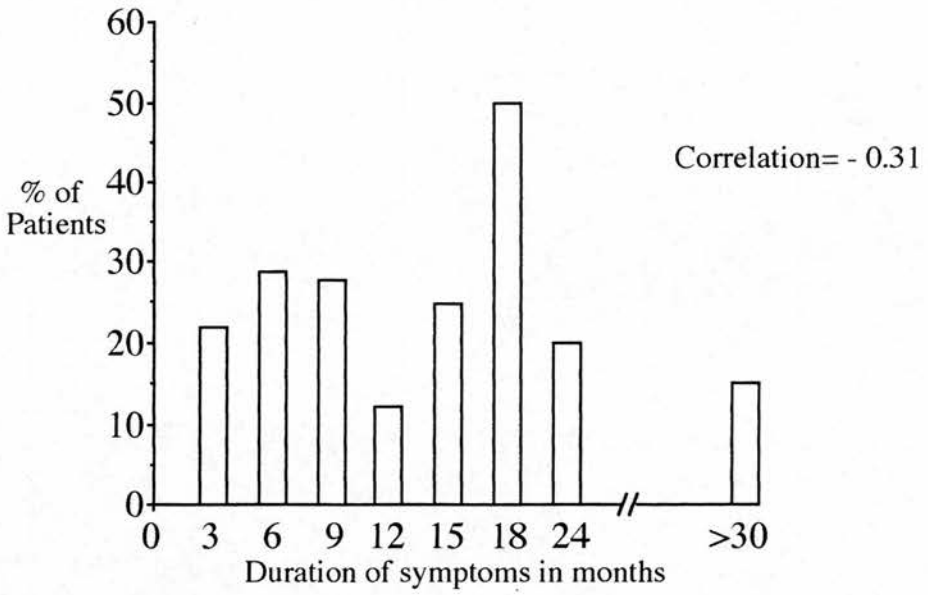

Fig 4. 155 Patients, grouped by the duration of their symptoms from 3 to more than 30 months, showed a negative correlation between the duration of symptoms and the presence of hepatic metastases.

Younger patients tended to have a longer history than older ones. The median age at presentation for those with a history of less than 4 months was 72 years and for those with a history of more than 4 months the median age was 67 years ($p<0.05$ Mann-Whitney U test). The median age of patients with metastases was also 67 and the median age for patients without was 72 years ($p<0.05$ Mann-Whitney U test) (*Fig 5.*).

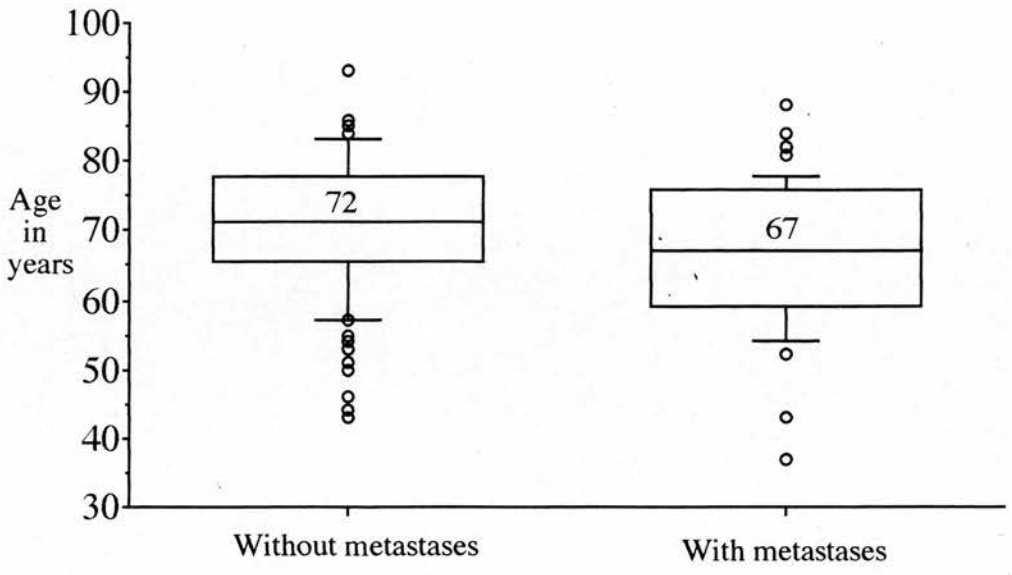

Fig 5. Patients with metastases were significantly younger at presentation than those without ($p < 0.05$ Mann-Whitney U test). The small circles o, represent values outwith the 10th and 90th percentile (represented by the ⊥, whiskers). The box contains the first to the third quartile. The bisection of the box represents the median value .

VI.B.4.d. Liver function tests

There was no significant difference in serum bilirubin values (median and range) in those with (7 mg/l range 3-34) and those without (8 mg/l range 2-41)metastases. The same was true for serum albumin between patients with (40g/dl range 30-49) and without (38g/dl range 28-58) metastases. There was a statistical difference in the levels of alanine amino transferase in the two groups ($p < 0.01$ Mann-Whitney U test), but the overlap was large (*Fig 6*).

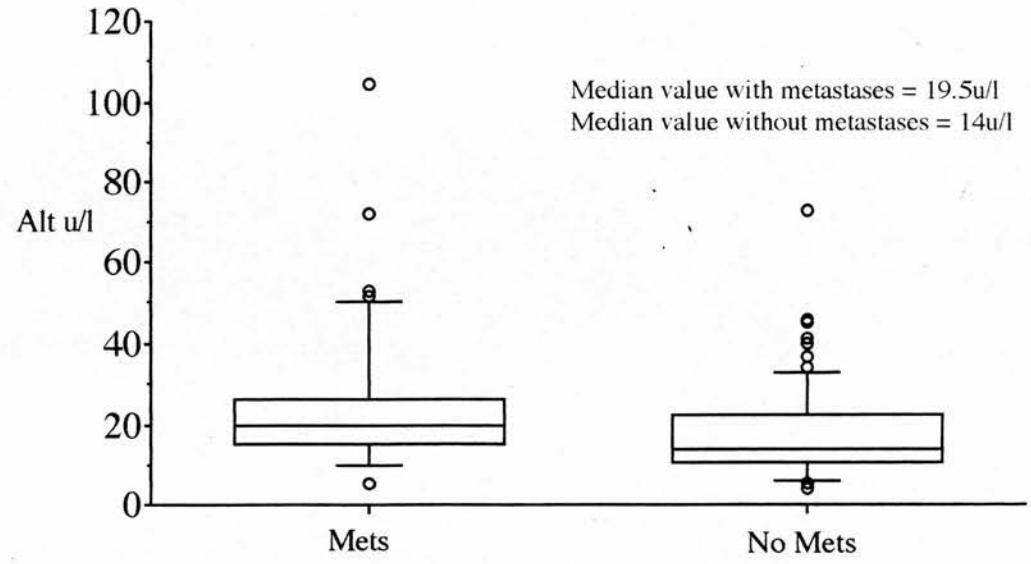

Fig 6. Box and whisker plot of alanine amino transferase values in patients with and without hepatic metastases.

Alkaline phosphatase was also significantly raised in patients with hepatic metastases ($p<0.05$ Mann-Whitney U test). The range in the two groups was large and there was overlap between the patients who did and those who did not have metastases (*Fig 7.*).There was no clinically useful cut-off point that could be used to indicate those patients with and those without metastases.

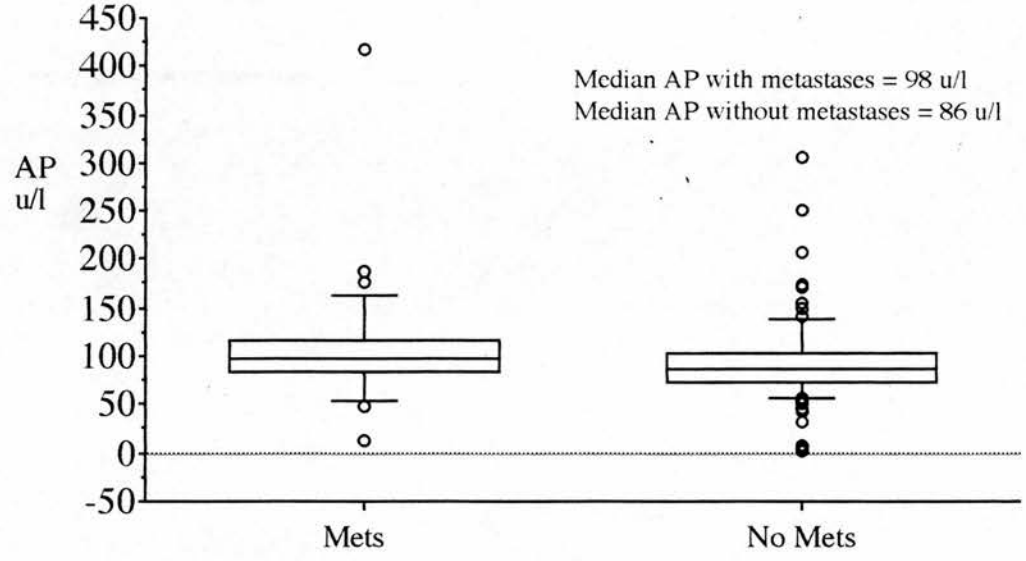

Fig 7. Box plot of alkaline phosphatase in patients with and without metastases ($p<0.05$ Mann-Whitney U test).

VI.C. Discussion

The most powerful predictor of outcome in the 24 months following surgery is the presence, or absence, of hepatic metastases at the time of operation (Finlay IG. 1983, 1988). The mean survival for patients with hepatic involvement is between 10 and 36 months in unselected series (Finan PJ, 1985; Wagner JS 1984) and few, if any, survive to five years without treatment. Survival can be improved by resection of hepatic metastases, to give five year survival of 25%-30% (Wagner JS, 1984; Coppa GF, 1985; Bengmark S, 1982). Thirty percent or more of patients may have metastases at the time of surgery, only 15% of which may be detectable by preoperative ultrasonography, or by palpation at operation (Finlay IG, 1986). During routine follow-up, these occult metastases will only become apparent when they cause symptoms unless routine DBCT or IOE scanning is undertaken. The identification of patients who have hepatic metastases at the time of presentation, may improve survival by identifying patients who will be suitable for hepatic resection.

Detection may be improved by performing IOUSS at the time of primary

surgery. This investigation is as accurate as IOE scanning in the detection of metastases at the time of operation and has high negative predictive value (97%). The values for sensitivity, specificity, positive predictive value and accuracy are similarly high at 93%, 99%, 98%, and 97% respectively. To have values for detection of all metastases of all sizes, as high as this seems to be unlikely to be true. The very high detection rates attributed to IOUSS are a reflection of the comparatively poor resolution of the other imaging techniques used in the routine follow-up of patients with colorectal cancer. If this group of patients was followed to five years instead of two it is likely that the false negative rate and the false positive rate for IOUSS would begin to climb and the overall figures for accuracy would come into line with other published data (Chapter II, *Table 3.*)(Charnley RM, 1991; Machi J, 1991). IOUSS did not interfere with the performance of the primary colonic surgery. Consultants readily agreed to the procedure and found the scans interesting and informative. Most were surprised in the early part of the study when the scanner picked up metastases which they could not detect by palpation. By the end of the study, the scan added no more than seven minutes to the operation time, although if a lesion was seen and biopsy attempted, a considerable amount of time could be added to the procedure depending on the exact site of the lesion. There were no post operative complications related to the IOUSS; this is in keeping with other series (above), to date there have been no reports of any morbidity related to the performance of intraoperative ultrasonography. IOUSS is a sensitive technique and detected a significantly larger number of the patients with metastases at the time of operation than palpation alone. This relates primarily to the ability of IOUSS to detect very small lesions (4 mm in this series) deep in the hepatic parenchyma. There is an absolute value for the minimum size of lesion that can be detected by either palpation or IOUSS, although exactly what this is remains unclear. IOUSS may detect very small lesions if they have an echogenic structure and a potential limit of 2 mm had been suggested (Charnley 1988). The detection of a 4 mm metastases within the substance of the liver in this series would appear to be in keeping with the level of resolution found by others (Rifkin MD, 1987; Thomas WM, 1987; Machi J, 1987,1991; Boldirini G, 1987; Makucchi M, 1987; Sheu J-C, 1985; Olsen AK, 1990; Clarke MP, 1989; Gozzetti G, 1988; Charnley RM, 1988,1989,1991). The echogenic profile of some metastases is so similar to that of the normal liver that even when the lesion is palpable and visible to the naked eye it may only be apparent by its mass effect on ultrasonography. If there are no boundaries of differing acoustic impedance between a metastases and the liver or within the metastasis itself, it will not be visible. Most metastases (80%) create a pseudo

capsule of compressed liver tissue and it is this which creates the anechoic halo of the classical 'Bulls eye' lesion (Marchal G,1985). This phenomenon is dependent on the growth pattern of the metastases and the response of the host.

Small, subcapsular metastases were not detected if the scanning head was placed directly over the lesion. These lesions were detected in two ways, palpation as part of the routine prior to scanning, and scanning the liver from both its superior and inferior aspect. Subcapsular lesions can also be detected by using a stand-off although its use is unwieldy and time consuming in practice.

Lesions seen on IOUSS were characterised in two ways: firstly by their appearance and secondly by biopsy. Although the appearance of a lesion is difficult to quantify there is no doubt that visual lesion recognition was very accurate. There was only one false positive lesion which was confirmed pathologically. This gives a false positive rate for the identification of metastases of 0.7%. In light of this it is reasonable to question the role of needle biopsy. Biopsy failed to confirm the presence of metastases in 3 of 9 patients. All 3 went on to develop metastases which were detected by IOE scanning during follow-up. This represented a 30% false negative rate for biopsy a higher rate than for IOUSS. In the past, biopsy has been seen as the gold standard for the identification of metastases, however, in this series the failure rate of targeted biopsy was so high as to make it an unreliable indication of the true nature of a lesion. The false negatives were caused both by sampling errors (because of the difficulty in gaining access to the liver through a low transverse abdominal incision) and reporting errors (interpretation of fine needle aspiration cytology samples from hepatic metastases may be very difficult). These factors are not a problem during hepatic resection when the liver is fully mobilised and a 'Tru-cut 'needle can be used for sampling

Hepatic anatomy in this series was found to be almost constant with only one patient displaying a congenital absence of the left portal pedicle. This confirms that the internal hepatic anatomy provides a very constant map by which areas of the liver can be identified (Bismuth H, 1982).

The Dukes stage was reported in 82% of the specimens and was shown to under stage the disease in 23% of these. Because Dukes is a method of reporting the actual physical appearance of the primary cancer, it can only give an estimate of stage and thus prognosis, the survival estimate having being gained from a population of patients who had a similar appearance of primary

disease.

The identification of patients who actually have metastases at operation increases the accuracy of the staging. In this series 3 : 10 Dukes A patients had metastatic disease at the time of operation. The level of metastatic disease in the Dukes B group was approximately 2 : 10 and for Dukes C over all approximately 3 : 10. From these data it would appear the percentage of patients with hepatic metastases at the time of operation in this small series was not correlated to the Dukes classification. As expected 3 : 10 patients had metastases present at the time of operation (Finlay IG, 1982).

Both pain at presentation and derangement of liver function tests were related to the presence of metastases but neither of these factors were absolute predictors of metastases. There was almost complete overlap of the values of liver function tests between the group with metastases and the group with no metastases. There was a slight negative correlation between the presence of metastases and the duration of disease symptoms (opposite to that which might have been expected). One theory of metastases suggests that with time a tumour develops its potential to metastasise (Fidler IJ, 1990), this is related to the number of specific genetic deletions that occur in the cells of the tumour with successive mitotic cycles (Sanchez J, 1986). The longer a tumour has been present the more metastases one might expect be present. In this series the opposite was true, patients who had long periods of symptoms prior to their operation were slightly less likely to have metastases than those with a short history. It is possible that within a generally old and frail population that the presence of the tumour was not related to the duration of abdominal symptoms. Another explanation would be that those with a long history had slow growing tumours which, by their nature, were less aggressive and therefore less likely to metastasise.

Duration of symptoms showed a slightly negative correlation to age at presentation: the mean age for patients with less than 4 months history was 5 years less than those with a longer history. It would appear from this that relative youth at presentation and short history are both negative prognostic factors and carry a higher risk for the presence of hepatic metastases.

Haemangiomas were detected from time to time. At the inception of the study it had been decided that lesions suspected of being haemangiomas on their appearance would not be subjected to FNA or 'Tru-cut' biopsy because of the possibility of producing intrahepatic haemorrhage. There were 4

haemangiomas correctly diagnosed in 3 patients. One large cavernous haemangioma was incorrectly diagnosed as a metastasis. This large lesion was resected and its nature confirmed on pathological section. There was no way of improving the diagnostic accuracy of IOUSS in the detection of haemangiomas without the use of ultrasonic contrast enhancement agents (Mattrey RF, 1982, Matsuda Y, 1986, Carroll BA, 1982).

VI.C.1. Technique

Intraoperative ultrasonography is a simple technique although there is considerable skill required to correctly interpret the results of the scans. In this series the principle investigator WFAM was trained by a specialised hepato-biliary surgeon (OJG) in the technique of intraoperative ultrasonography and in the recognition of metastases and other lesions within the liver. That the accuracy of IOUSS was high and remained so was due to the level of training prior to the inception of the study and the quality of the images which can be obtained by IOUSS equipment. Training courses and training manuals are currently available, as are echo cameras which provide excellent image quality. Such equipment would allow any general surgeon to perform IOUSS and achieve acceptable results.

Intraoperative ultrasonography offers an alternative to enhanced CT scanning in the detection of metastases at the time of operation. Its limitations are that; it can only be performed at laparotomy and it is a dynamic technique and therefore operator dependant. It is also difficult to capture the subtle changes of an infiltrating tumour on a still images. The remaining disadvantage of the technique is that it is a new skill which must be learned; either by a surgeon in ultrasonography, or by the radiologist in the interpretation of operative scans. In British practice it seems likely that the use of ultrasonography by the surgical community will increase. It is equally unlikely that there will ever be enough radiologists to support a service of intraoperative ultrasonography for all patients coming to operation with colorectal cancer. Intra-operative ultrasonography will remain in the domain of the surgeon.

By using a combination of intraoperative ultrasonography at the time of surgery and IOE scanning in the follow up period, it is possible increase the detection of hepatic metastases. There are no data yet available to suggest that early detection by either intraoperative ultrasonography or by enhanced CT scanning of resectable hepatic metastases will improve survival. In the past, patients who have had hepatic resection are those who have survived for at a period of

time with a small number of hepatic metastases. These patients may represent a self selected group who already have a better prognosis. The patients in this series who were found to have hepatic metastases at operation and who were not pre-selected in the same way did not have a survival benefit from resection. It seems likely that there is a balance between early detection and surveillance in that patients who have potentially resectable hepatic metastases at operation should have a period of surveillance following their surgery to allow other occult metastases in the liver to declare themselves prior to resection. They should then be restaged by laparoscopy and laparoscopic ultrasonography prior to resection.

Of the 155 patients who were operated on for colonic malignancy in this series 8 had other primary pathology. There was marked variation in the level of preoperative investigation carried out by different clinicians. Up to 29% of patient with a colonic malignancy have polyps elsewhere in the colon and 4.5%-9% have synchronous malignancy (Tate JJT, 1988). It is important that these lesions are detected before operation and removed. Failure to do so may expose the patient to the risk of further primary tumour as well as the risk of metastases. There is little to be gained by resecting small volume intrahepatic metastases in a patient who may have an undetected, synchronous cancer in the colon.

Chapter V11

Carcinoembryonic antigen: Its relationship to the presence of hepatic metastases.

VII.A. Introduction

Described by Gold and Freedman in 1965, Carcinoembryonic antigen is a tumour marker whose elevation, in serum samples drawn from patients with colorectal malignancy, may be related to the presence of primary or recurrent carcinoma (Finlay IG, 1983; Sugarbaker PH, 1976). However, it lacks the specificity and accuracy required to stand alone as a useful screening test for primary malignancy of the colon (Go VLW, 1976; Goldenberg DM, 1981; Tormey DC, 1982; NIC, 1981) and its exact role in this context has, unfortunately, remained unclear. Serum CEA may be elevated in a number of benign and malignant conditions (Lowenstein MS, 1978; Stevens DP, 1973) and may also remain in the normal range in the presence of colorectal cancer (Neville AM, 1978; Minton JP, 1985; Martin EW, 1976). Repeated assay of serum CEA following resection for colorectal cancer can give an indication of recurrent disease (Wanebo HJ, 1978; 1981 Mach JP, 1978; Mackay AM, 1974). Some authors have shown serum CEA elevation to be a late event in recurrence and therefore an inappropriate criteria for deciding when to initiate treatment (Sugarbaker PH, 1976; Herrera MA, 1976; Finlay IG, 1983; Minton JP 1985). Serum CEA is the most commonly used tumour marker in relation to colorectal cancer (Sikorska, 1988).

Serum CEA estimation is used in a number of contexts: diagnosis of primary colorectal cancers, immediate assessment of completion of resection and the detection of recurrence during follow up.

In this chapter three groups of patients are considered. In the first group, consisting of patients with known hepatic metastases from colorectal cancer, the relationship of serum CEA to the presence and resectability of hepatic metastases is defined. In the second group, consisting of patients presenting with colorectal cancer, the relationship of serum CEA to the presence of hepatic metastases is defined. The information from groups 1 and 2 is used to identify a level of serum CEA which indicates the presence of recurrence and this is tested on a third group of patients in long-term follow up.

VII.B. Aim

The objective of this chapter is to investigate the relationship of serum levels of CEA, determined by radio immunoassay, with the presence of primary colorectal cancer, hepatic metastases from colorectal cancer and the presence of locally recurrent disease. This has been achieved by evaluating the presence or absence of hepatic metastases and local recurrence in three groups of patients following primary resection for colorectal cancer.

VII.C. Patients and Methods

The data from three groups of patients are examined in this chapter;

- Group 1. Patients presenting with hepatic metastases being considered for hepatic resection (discussed in chapter IV)

- Group 2. Patients who have been staged by IOUSS and / or IOE scanning at the time of, and following, curative primary resection for colorectal cancer (discussed in chapter V and VI).

- Group 3. Patients who have been followed up in a dedicated colorectal clinic following curative resection of colorectal cancers (not previously discussed).

VII.C.1. Group 1

The group consisted of 60 patients, (36 male) average age 61 (28-84) with colorectal hepatic metastases. All of these patients had been extensively investigated and the exact extent of their recurrent disease recorded. In particular, the presence of hepatic metastases, pulmonary metastases and local recurrence was known. The staging of these patients is described in chapter IV. The results of the investigations related to the serum CEA levels are described below.

VII.C.2. Group 2

This group consisted of one hundred and forty seven patients who have had laparotomy, IOUSS and IOE scanning of the liver at the time of their presentation with colorectal cancer. Fifty two of these patients had repeated IOE scans in the follow up period and serum CEA was measured at the time of each scan. A number of patients continued to have serum CEA samples taken after their last IOE scan as part of their routine follow up and these results have also been included. The longest follow up in this group of patients is 50 months. These patients have been described in chapters V and VI.

VII.C.3. Group 3

This group consisted of two hundred and sixty five patients admitted to the Western General Hospital, Edinburgh (WGH), between 1988 and 1990, who underwent a potentially curative resection of colorectal cancer, identified from the Lothian Surgical Audit (LSA). The following were excluded from the series: patients with less than one preoperative and two postoperative CEA estimations, a palliative primary resection of their primary cancer or incomplete follow up data. The policy of this unit has been to follow-up all patients who had a potentially curative resection by repeated serum CEA estimation and clinical examination. One hundred and twenty five patients remained to be studied, their median age was 69 years (range 42-91); 65 were male.

Patients in group 3 were followed up in a long-term manner with regular clinical review (4 visits in the first year, three in the second and annually or better in the following years). A full history was taken at each clinic visit followed by physical examination, rectal examination, faecal occult blood testing, rigid sigmoidoscopy and blood samples were taken for serum CEA estimation.

VII.C.3.a. Method

The methods for group 1 and 2 have been discussed and are summarised.

Patients in group 1 were admitted to the Hepatobiliary Unit of the Royal Infirmary of Edinburgh for consideration of resection of known hepatic metastases. Each patient underwent a series of investigations to ascertain the resectability of their disease. These included CT scanning, IOE scanning angiography and IOUSS (in patients selected for resection). The number of hepatic segments involved by metastases was known in each patient as was the presence of local recurrence and the serum CEA.

Patients in group 2 had intraoperative ultrasonography of the liver performed at the time of primary resection of their colorectal cancer. These patients were then followed up by sequential IOE scanning, clinical review, sequential serum CEA estimation and by contact with their GPs.

Group 3. The clinic letters of these patients were interrogated using a standard format and the information obtained tabulated for analysis. The serum CEA results for these patients were supplied from the serum CEA database which is maintained by the Edinburgh University department of clinical chemistry immunoassay section (JS, CS).

Comparison and analysis was then performed using Statview SE + Graphics™ (Abacus Inc.).

VII.C.3.b. Serum CEA estimation

All serum CEA estimations were performed by the Department of Immunochemistry by radio-immunoassay under the direction of JS and CS. The results of estimations are compared to both internal and national external controls to ensure continuity of the assay. The upper limit of normal in this laboratory is 60u/l. In this assay, a level of 100u/l (using International Standard IRP 73/601) corresponds to approximately 10μg/l of CEA.

VII.D. Results

VII.D.1. Group 1

VII.D.1.a. Serum CEA and colorectal liver metastases

Serum CEA was measured in all 60 patients when they presented for restaging. Patients can be grouped at various cut-off points for CEA; 47 (78%) had a serum CEA of > 60u/l, 44 (73%) had a serum CEA of > 100u/l, 41 (68%) had a serum CEA of >160 u/l and 26 (43%) patients had a serum CEA of ≥ 1000 u/l. The results for serum CEA estimation at the time of presentation for these 60 patients was not normally distributed (*Fig 1.*)

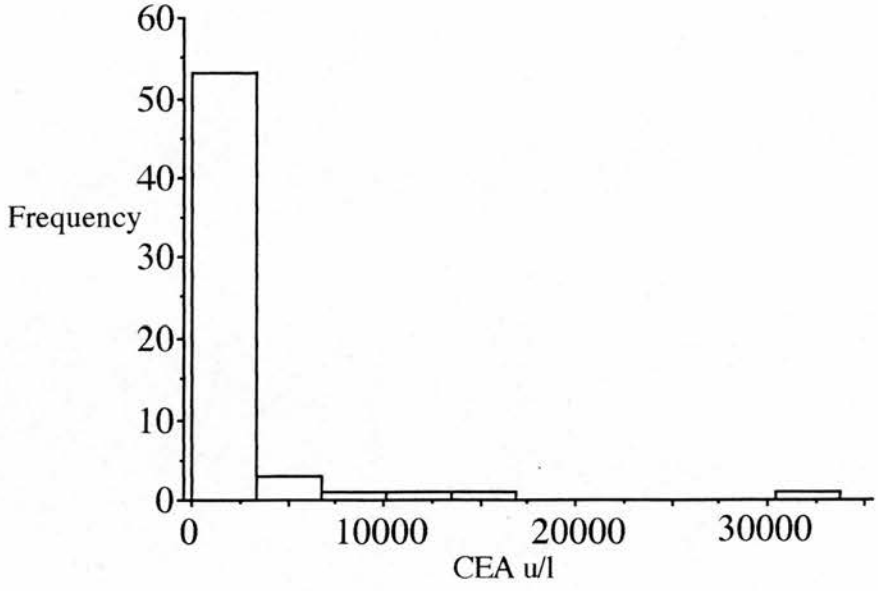

Fig 1. The distribution of serum CEA value in u/l at presentation with recurrence for patients in group 1 is skewed to the right (Skewness = 5) (This data is not suitable for parametric analysis).

In order to produce a more normal distribution curve, a logarithmic transformation was undertaken on the serum CEA values at presentation with recurrence for the patients in group 1 (*Fig* 2.)

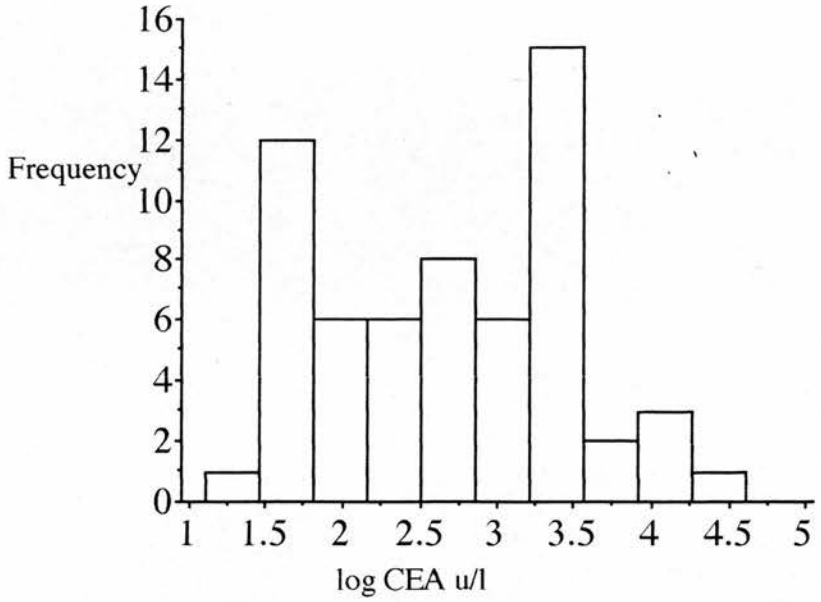

Fig 2. Logarithmic transformation of serum CEA u/l at presentation with hepatic metastases for patients in group 1 (Skewness -0.06). A logarithmic transformation reduces the skew of the data However, it also reveals an apparently Bi-modal distribution. This may be expected, as 20 % of colorectal cancers do not produce CEA. The first peak appears in the second column which includes the value serum CEA of 30u/l. (log = 1.47), 30u/l is the lowest reported value for serum CEA in our laboratory . Values lower then 30u/l are reported as serum CEA ≤ 30u/l unless an absolute value has been requested which was not the case in this study, and because of this the left hand tail of the distribution has been distorted. This distribution of results is not suitable for parametric analysis..

Because of the lack of normal distribution of the serum CEA values, non-parametric analysis has been used unless otherwise stated. A parametric regression analysis was performed on the logarithmic transformation of serum CEA and age at presentation.

VII.D.1.b. The relationship of Dukes stage at presentation to serum CEA at recurrence

The Dukes stage of the primary cancer at presentation was recorded in 45 patients (*Table 1*). Unfortunately the serum CEA at presentation of the primary cancer was not available for any of the patients in group 1.

Dukes stage	Number of patients	Median CEA u/l
A	2	1850
B	16	598
C	25	284
D	2	1015
Total	45	527 (13-53600)

Table 1 Serum CEA values at presentation with hepatic metastases for 45 patients in whom the Dukes stage of their original tumour was known. The serum CEA values do not conform to a normal distribution (Skewness = 6) and so nonparametric analysis has been used. There is no significant difference in the serum CEA value for any of Dukes stages compared to the rest (Kruskal-Wallis , p = 0.5163)

There was no significant relationship between the level of serum CEA at recurrence and the Dukes stage of the primary tumour. The site of the primary cancer was also recorded and this has been related to the serum CEA level at the time of presentation with hepatic metastases (*Fig 3*). There was no significant difference in the serum CEA level (at the time of recurrence) between metastases originating from any one primary site and another, particularly there was no difference between cancers from the right colon and cancers from the left colon or rectum.

The level of serum CEA at presentation was significantly lower in those patients who underwent successful hepatic resection compared to those who did not (*Fig 4.*).

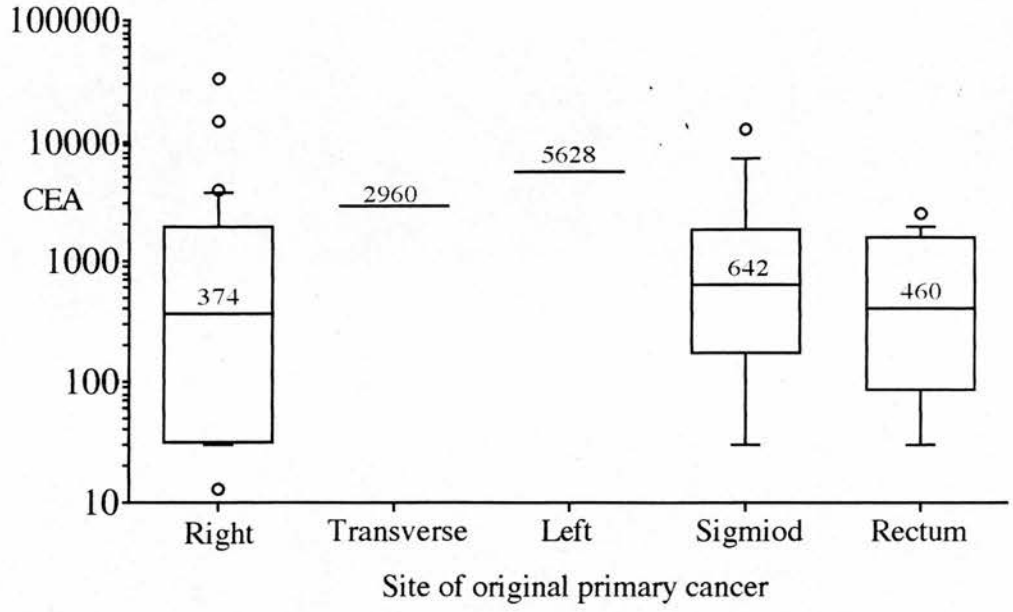

Fig 3. Box plots of serum CEA u/l and the anatomical site of the index primary cancer. There is no significant difference in the levels of serum CEA found at recurrence and the original site of the primary cancer . The median value for each site is above the horizontal transection (Kruskal - Wallis p=0.27)

The median value for patients with irresectable disease corresponds to the value at which serum CEA best determines the resectability of disease. A serum CEA of ≤ 1000 u/l has an accuracy of 58% in determining resectability (*Fig 5.*)

The number of hepatic segments involved with tumour was also recorded. A multiple nonparametric analysis of this data revealed no significant difference in the levels of serum CEA at presentation between those who had one segment involved and those who had all eight segments involved. There was, however, a positive correlation between the level of serum CEA and the number of segments involved with metastases at the time of staging, which did not reach statistical significance. The number in each of the groups was small and the variation in serum CEA values is large (*Fig 6.*). As the number of segments involved was used as one of the criteria for resection, there was a positive relationship between more than four segments involved and the diagnosis of irresectable disease.

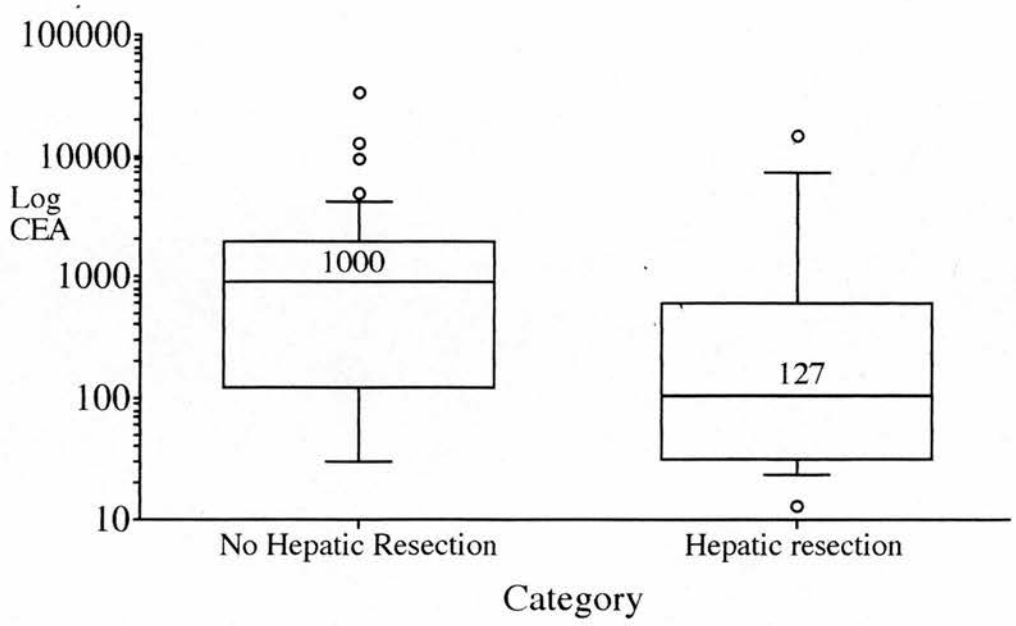

Fig 4. Box plot of serum CEA (plotted on a log scale) for patients who did and did not have a successful hepatic resection for colorectal metastases. Patients who had a successful resection had a median serum CEA value of 127 u/l, those who did not had a median value of 1000 u/l (p< 0.05 Mann-Whitney U test)

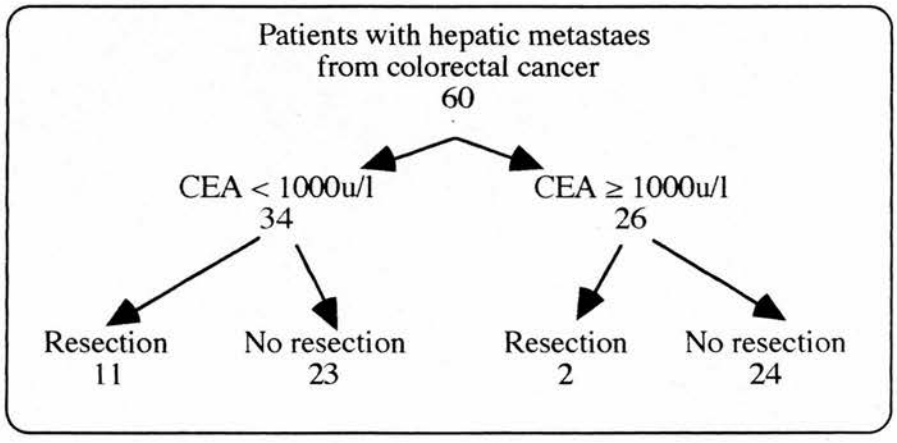

Fig 5. serum CEA can be used to predict the presence of resectable hepatic metastases in patients who have had a curative resection of their primary colorectal cancer. A serum CEA value of < 1000u/l has a sensitivity of 85%, specificity of 51%, positive predictive value of 32%, negative predictive value of 92% and an overall accuracy of 58% in identifying successful hepatic resection as an outcome. Patients with a serum CEA of < 1000u/l are more likely to have a successful hepatic resection (Chi sq = 5.28 1df, p < 0.05)

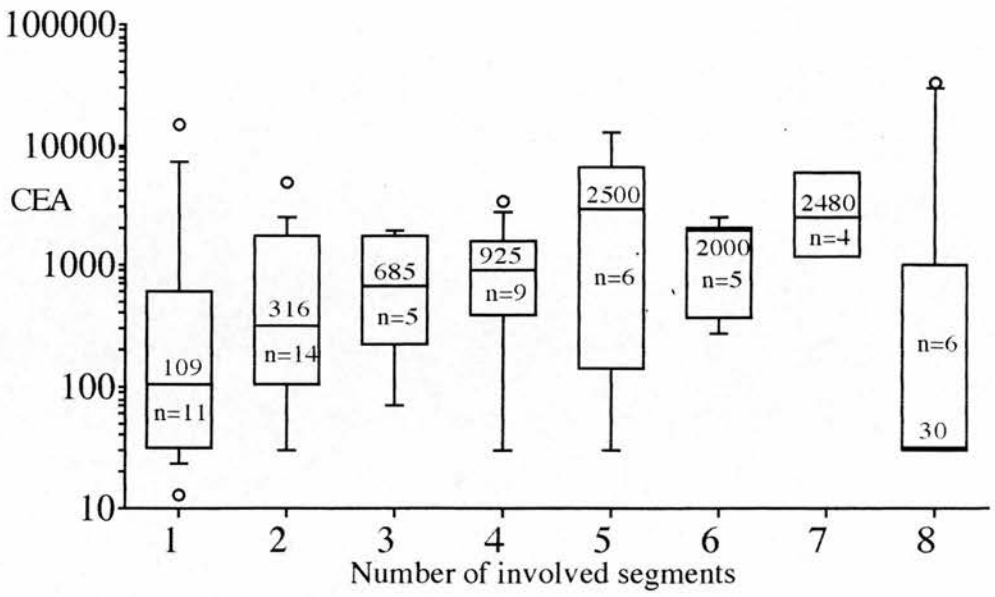

Fig 6. Box plot of the number of hepatic segments involved by metastases against the serum CEA u/l (on a logarithmic scale) at presentation.

There is a trend for the serum CEA to rise with the number of segments involved by tumour. The value "n" in each box indicates the number of patients in each group. The median value for each group is printed within the box. There is no significant correlation between the serum CEA and the number of segments involved using the Kendall rank correlation coefficient ($\tau = 0.2$ $p = 0.083$). It would appear that there is a correlation between the number of segments involved and the median serum CEA for each group, except for the patients with 8 segments involved. By removing the data for patients with 8 segments involved, the value for τ increases to 0.3 , $p = 0.0027$, indicating a stronger and significant relationship. Selective analysis of this type may be misleading. However common sense would suggest that the relationship for patients with 1 - 7 involved segments should hold true for patients with 8 segments involved.

There is no significant relationship between the log of the serum CEA at presentation and the age in years of the patient (*Fig 7*). Because of the normal distribution of age and patients with colorectal cancer and the near normal distribution of the log of the serum CEA, the coefficient of regression r is quoted. This fails to demonstrate a significant correlation. These data were also analysed using the Kendall rank coefficient, this being a less powerful test, but more accurate for data which tends not to have a normal distribution. This again shows that there is no significant relationship between age at presentation with hepatic metastases and serum CEA levels ($\tau = 0.00005$ $p = 0.5$).

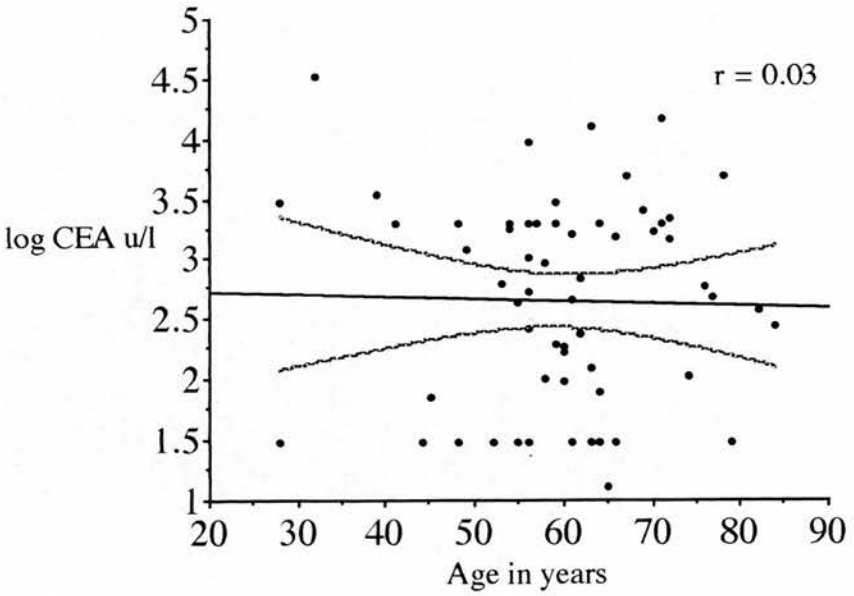

Fig 7. Regression analysis of the age at presentation and the log of the serum CEA at presentation r = 0.03 p = 0.8 (Fishers z-transformation) the 95% confidence intervals are indicated by the faint lines.

The lag time from primary resection and the level of CEA at recurrence are also independent (*Fig 8.*).

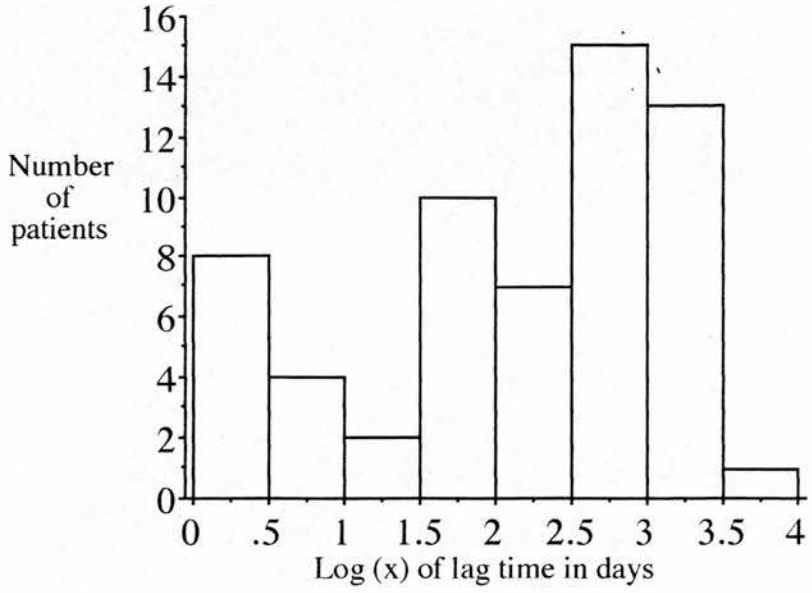

Fig 8. Initial examination of the lag time from primary resection to detection of recurrence reveals that the data were skewed to the right.

In fact, logarithmic transformation revealed that there was a bi-modal distribution. A very early peak corresponding to patients who had their hepatic metastases detected at the time of primary surgery (mean lag of 1.77 days) and a second peak corresponding to patients who had been detected during routine follow-up (mean lag of 562 days). This distribution confirmed that this data had to be analysed using a non-parametric test. There was no significant relationship between the number of days from diagnosis to the detection of recurrence and serum CEA at recurrence (Kendall rank coefficient $\tau = 0.07$, $p = 0.4217$).

VII.D.2. Group 2

Sixty eight of the 147 patients who had colorectal cancer (46%) had a serum CEA at presentation greater than 60 u/l. The frequency distribution of the serum CEA u/l at presentation did not form a normal distribution and could not be easily transformed to do so (*Fig 9. and 10.*).

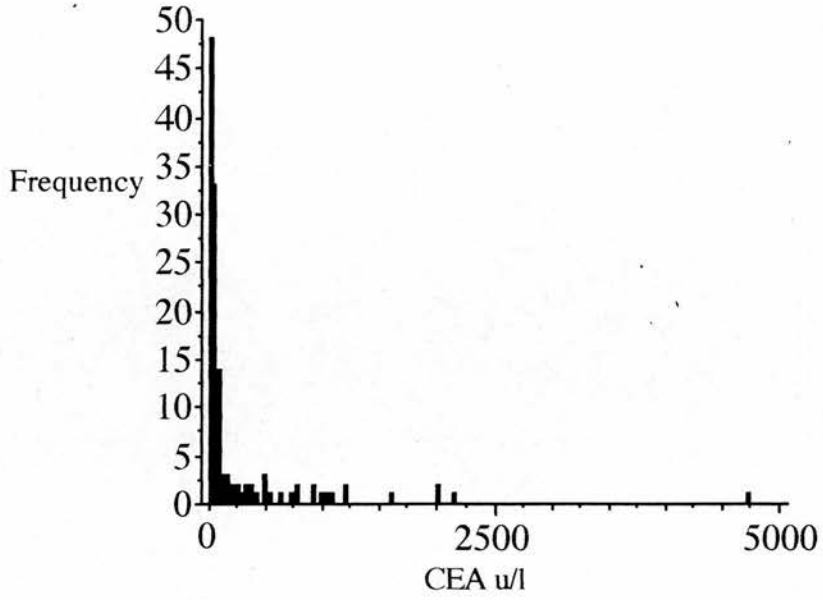

Fig 9. Frequency distribution of the serum CEA levels at presentation for patients with colorectal cancer, median 50u/l range ≤ 30 u/l to 4740 u/l . This distribution is skewed to the right (skewness = 5).

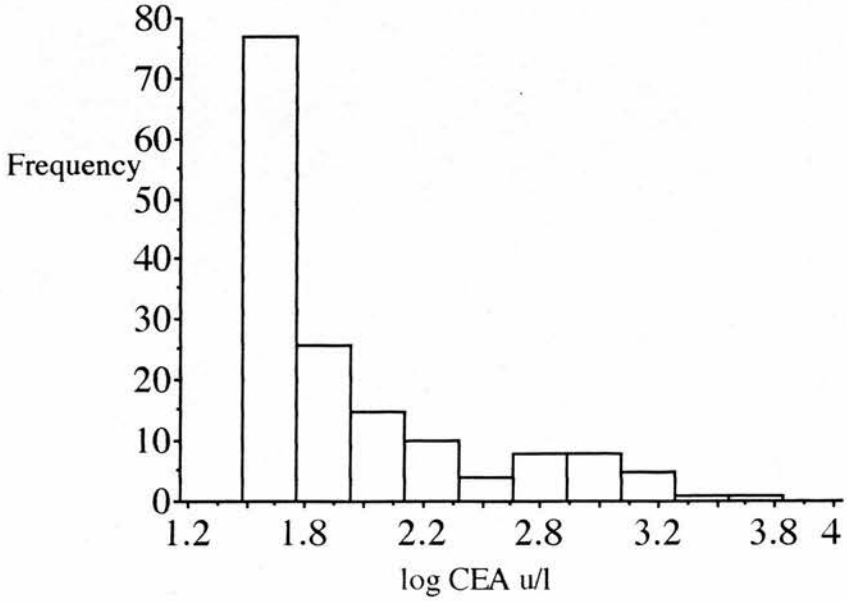

Fig 10. A logarithmic transformation of the serum CEA at presentation of patients for primary resection of colorectal cancer fails to produce a normal distribution. The histogram remains skewed to the right (skewness = 1).

Because of the skewed nature of the results of the serum CEA estimations, non-parametric methods of statistical analysis have again been used for this section. In a comparison of the level of serum CEA at presentation independent of the presence of metastases, there was no significant difference in the level of serum CEA when related to the anatomical site of the primary cancer (*Table 2.*). There was a wide range of serum CEA and few significant differences in the groups (Multiple analysis of significance ANOVA).

Site of primary tumour	Number of tumours	Median serum CEA(range)
Caecum	25	55 (30-1090)
Ascending colon	7	86 (30-389)
Hepatic flexure	3	30 (30-545)
Transverse colon	9	30 (30-1200)
Splenic flexure	4	466 (30-4740)
Descending colon	6	36 (30-42)
Sigmoid colon	35	45 (30-2000)
Rectum-Above reflection	5	30 (30-1200)
Rectum-At reflection	6	92 (30-1000)
Rectum-Below reflection	47	55 (30-2150)
Total	147	51 (30-4740)

Table 2. The site of primary cancers in 147 patients having resection for colorectal cancer. The mean and range of serum CEA values were calculated for each of these groups. These have been compared using the ANOVA multiple comparison of significance. The serum CEA levels for cancers of the splenic flexure were significantly higher than all of the other sites (p = 0.05 Fishers PLDS) ,there is no significant difference in any of the other groups The sample size is probably too small for this test to be reliable.

Dividing the groups into right sided and left sided cancers (the point of division being splenic flexure cancers to the right, and descending colon cancers to the left), there was no significant difference in the serum CEA values with respect to site (p = 0.94 Mann-Whitney U test).

In this series (group 2), there was no significant difference between the serum CEA levels for Dukes A, B, C (p= 0.47 - 0.85 multiple Mann-Whitney U tests).

There were 10 patients who had a serum CEA of greater than 1000 u/l; 6 of these had hepatic metastases. Of the remaining 4, 2 had carciomatosis peritonei, one had locally advanced but resectable disease and one had a curative resection of a Dukes 'B' colonic cancer.

All patients were staged and the presence or absence of hepatic metastases was determined at the time of primary resection by IOUSS and during the follow up period by IOE scanning. Patients were grouped into those who had metastases (43 patients) and those who did not (104 patients) (*Fig 11*). The serum CEA was significantly higher at presentation for patients with metastases than for those without ($p < 0.05$ Mann-Whitney U test) . The range in the two groups was still large and the groups overlapped completely.

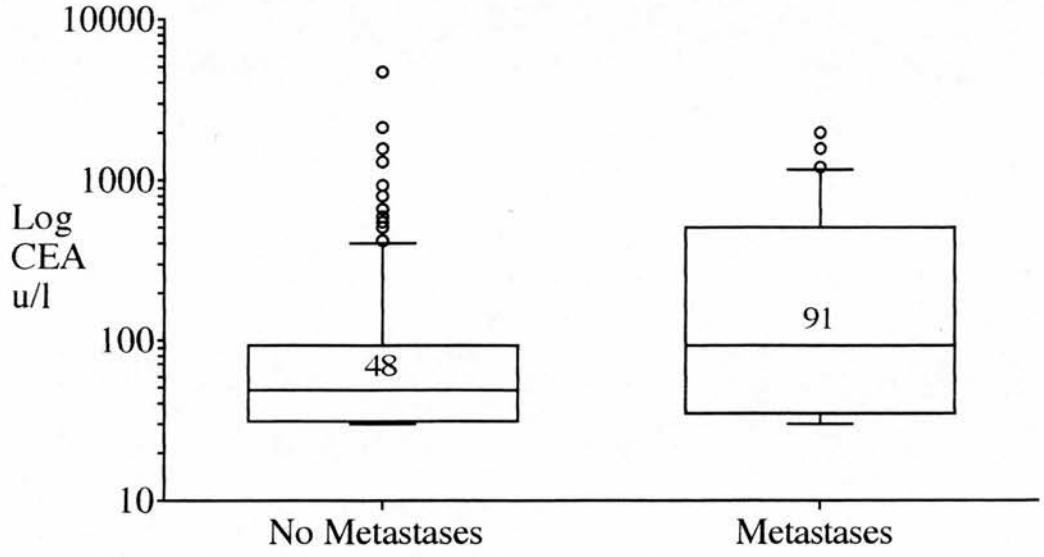

Fig 11. Log serum CEA u/l at presentation for 43 patients with and 104 without hepatic metastases, prior to resection of the primary tumour. Patients with hepatic metastases had a significantly higher serum CEA at presentation than those without.

Of the 43 patients with metastases, 18 (42%) had a serum CEA at presentation of greater than 100 u/l; 26 (25%) of the 104 patients without metastases had a serum CEA of greater than 100u/l (*Fig 12* . *Table 3*).

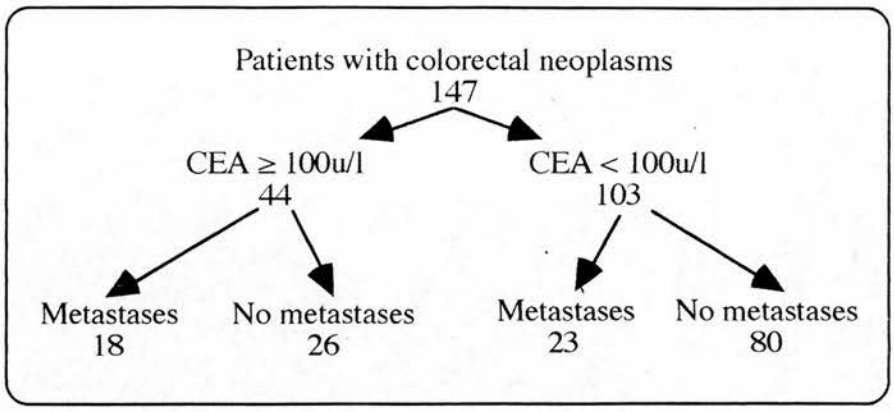

Fig 12. Algorithm for the detection of hepatic metastases at the time of presentation by determination of the plasma CEA. A cut off point of 100 u/l has been used to indicate metastases being present.

Parameter	Percentage
Sensitivity	44%
Specificity	75%
Positive predictive value	41%
Negative predictive value	78%
Overall accuracy	67%

Table 3. Accuracy of CEA ≥ 100 u/l in predicting the presence of hepatic metastases in patients presenting with colorectal cancer.

Patients with a serum CEA level of more than 100 u/l are significantly more likely to have hepatic metastases (Chi sq. = 5.29 1df $p < 0.05$).

To determine if the absolute level of which serum CEA is likely to indicate the presence of hepatic metastases in patients presenting with colorectal cancer multiple calculations were performed with cut off levels above and below 100 u/l (*Table 4. and Fig 13.*). An analysis was carried out using four fold contingency tables to calculate a value for χ^2 for each of the combinations of true positive, false positive, true negative, false negative for a given value of serum CEA in determining the presence of hepatic metastases. Yates correction was not applied. This gives the following results.

Calculation of Chi sq for various values of CEA in the determination of the presence of hepatic metastases.

	Hepatic metastases	No hepatic metastases	
CEA > X	TP	FP	TP+FP
CEA < X	FN	TN	FN+TN
	TP+FN	FP+TN	TP+FP+FN+TN

True positive = TP
True negative = TN
False positive = FP
False negative = FN

$$\text{Chi sq} = \frac{(TP \times TN - FP \times FN)^2 (TP+FP+FN+TN)}{(TP+FP)(FN+TN)(FP+TN)(TP+FN)}$$

Fig 13 . Multiple calculations of Chi sq were made using this formula.

	Serum CEA ≥ level in u/l										
	60	80	100	120	140	160	200	250	500	750	1000
Sensitivity	59	54	44	41	41	41	37	32	22	17	15
Specificity	58	69	75	80	81	83	85	87	92	93	96
PPV	35	40	41	45	46	49	48	48	50	50	60
NPV	78	79	78	78	78	79	78	77	75	74	74
Accuracy	59	65	67	69	70	71	71	71	72	72	73
χ^2	3.5	6.4	5.3	7.2	8.0	9.8	8.2	6.8	4.9	3.8	5.5

Table 4. Multiple estimations of the accuracy of serum CEA in the determination of patients with hepatic metastases from colorectal cancer. Accuracy continues to increase as the serum CEA level is increased, at the expense of sensitivity. The highest value for χ^2 (9.77) occurs at a serum CEA level ≥160u/l. This is the optimum level of serum CEA at which to determine patients who have and have not got hepatic metastases, prior to colonic resection .

A serum CEA value of ≥160u/l is an accurate indicator of patients who have hepatic metastases at the time of primary resection (*Fig 14*) (Chi sq 9.8 1df, p < 0.01)

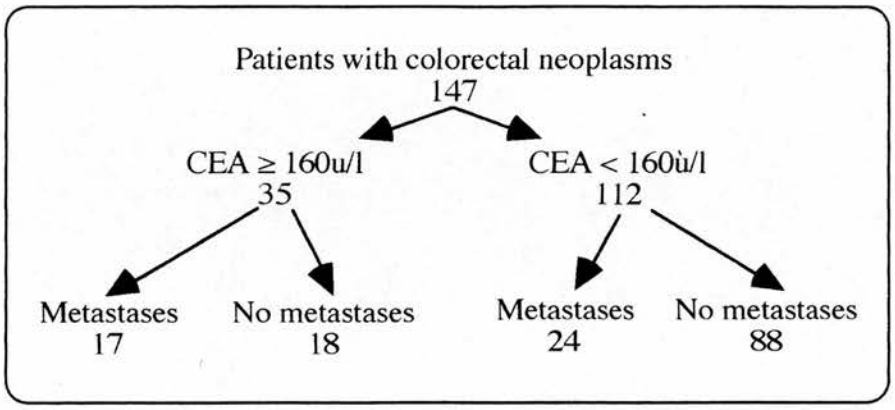

Fig 14. Serum CEA at a level of 160 u/l is an accurate and sensitive indicator of patients with colorectal liver metastases.

There were 52 patients who had more than one estimation of serum CEA in the follow-up period. Twelve of the 52 had metastases, 2 of the 12 had no elevation of serum CEA above 30 u/l at any time, 6 had no elevation above 100u/l at any time and 6 had elevation of serum CEA ≥ 100 u/l associated with the appearance of hepatic metastases. There were 5 patients with a serum CEA of more than 160u/l in follow-up all of whom had metastases. There were 40 patients who did not have metastases of whom 1 had a serum CEA of greater than 160 in the follow up period. The plots for the patients who had and those who did not have hepatic metastases are drawn below (*Fig 15, 16,*) to show the difference in trend of serum CEA in the two groups.

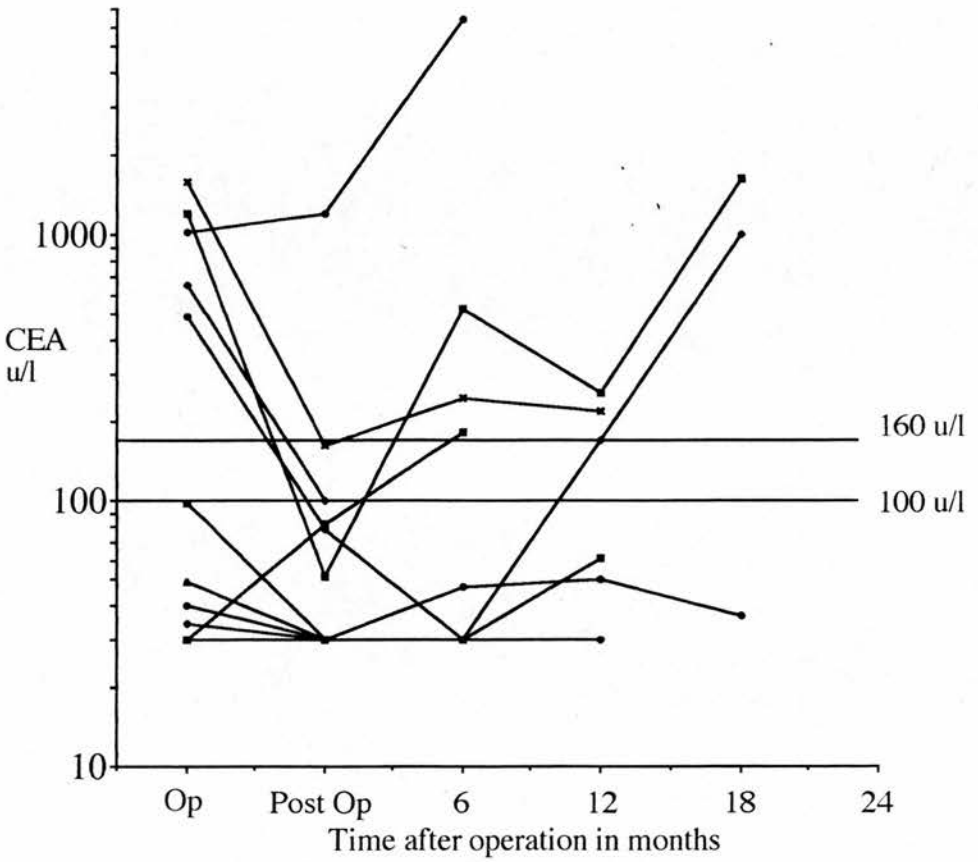

Fig 15. Patients following operation in whom there was evidence of metastases on IOE scanning. The serum CEA is plotted on a log scale with the cut off levels of 100 u/l and 160 u/l indicated by faint horizontal lines. There is very little difference in the accuracy of serum CEA at the 100 u/l and 160 u/l in the determination of which patient have and have not got metastases during follow up .

There were 40 of the 52 in whom there was no evidence of hepatic metastases. Four had a serum CEA of greater than 100 u/l in the follow up period. Only one patient showed a rapid rise in serum CEA to 204 u/l. This was the final estimation in this patient and was associated with a normal IOE scan.

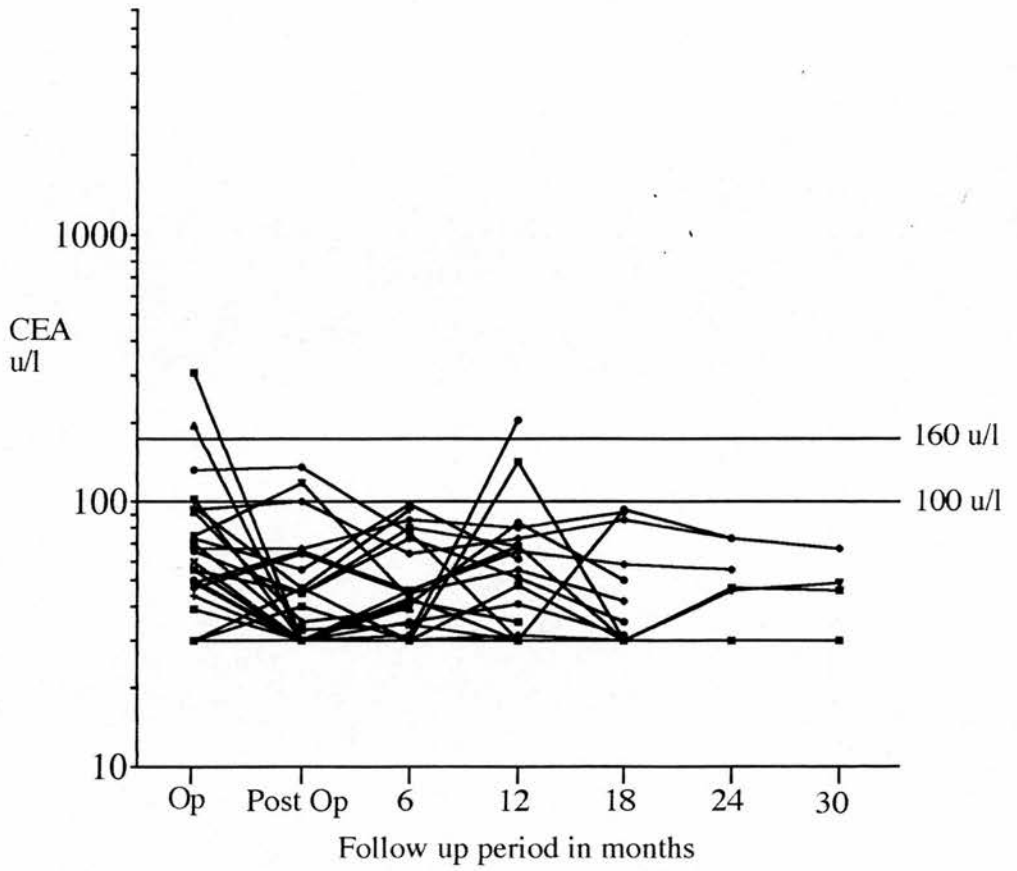

Fig 16. Patients following operation in whom there was no evidence on IOE scanning of hepatic metastases.

The accuracy of serum CEA in determining the presence of hepatic metastases in these patients is calculated at the 100 u/l and 160 u/l levels (*Fig 17* , *Fig 18* , *Table 5.*).

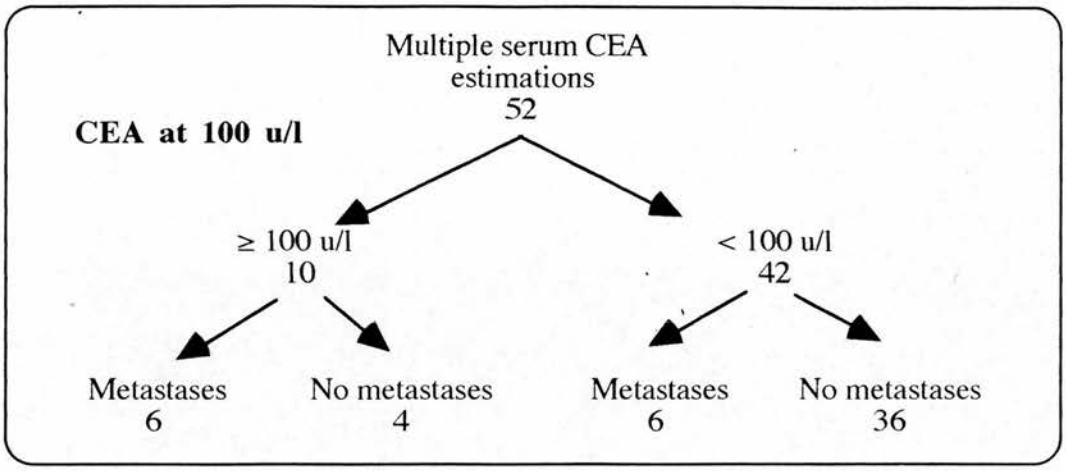

Fig 17. Serum CEA at 100 u/l in the determination of metastases in the follow up period.

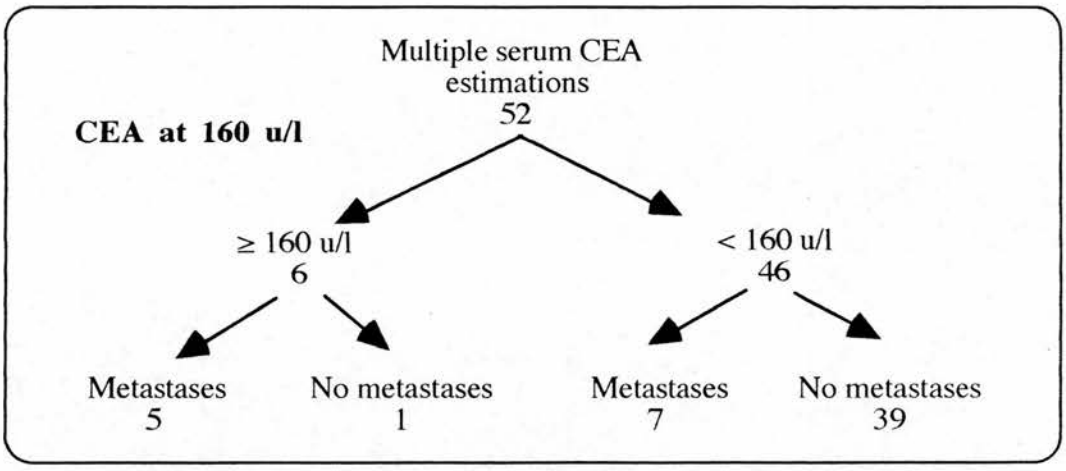

Fig 18. Serum CEA at 160 u/l in the determination of metastases in the follow up period.

Parameter	**serum CEA of 100u/l**	**serum CEA of 160u/l**
Sensitivity	50	42
Specificity	90	97
PPV	60	83
NPV	86	85
Accuracy	81	85

Table 5. Serum CEA at the 100 u/l and 160 u/l in the determination of the presence of hepatic metastases in 52 patients . The 160 u/l level gives a 7% improvement in specificity, a 23% improvement in PPV and a 4% increase in accuracy, at the expense of a 8% fall in sensitivity and a 1% fall in NPV.

The elevation of serum CEA to ≥ 160 u/l is 85% accurate (Chi sq = 13.87 1df, $p < 0.001$) in the identification of patients who have hepatic metastases. Analysis of patients in group 1 has shown that patients with a serum CEA of <1000 u/l are more likely to have resectable disease, so patients who have a serum CEA of between 160 u/l and 1000 u/l are more likely to have resectable hepatic metastases than patients with results outside this range.

VII.D.3. Group 3

There were 125 patients in this group. The median duration of follow up was 28 months (3 - 60). Dukes stage at presentation was recorded in 97 patients as follows: A - 10, B - 27, C - 38, D - 22.

Various levels of cut-off for CEA have been considered in this group of patients. There were 60 patients in whom the serum CEA rose to more than a cut-off of 60 u/l on at least one occasion. Forty eight of these patients had evidence of recurrent disease, 27 had evidence of hepatic metastases. Of the remaining 65 patients, 5 (two with hepatic metastases) who developed recurrence with no elevation of serum CEA above 60u/l. Serum CEA level rose to greater than a cut-off of 100 u/l on at least one occasion in 54 patients, 46 of whom developed recurrent disease of the remaining 71 patients 7 developed recurrent disease. A rise in the serum CEA to 100 u/l was a significant indicator of recurrent disease (Chi sq = 71.26 1df, $p < 0.001$). serum CEA rose to a level of greater than a cut-off of 160 u/l on at least one occasion in 40 patients, 34 of whom had evidence of recurrent disease. Serum CEA did not rise to more than 160 u/l in 85 patients, 19 of whom had recurrent disease. Six of the 7 patients who had no post operative elevation in their CEA had no elevation of serum CEA prior to their primary colonic resection. In 38 patients, serum CEA elevation preceded, clinically apparent, recurrent disease. In 16 patients, staging investigations were instigated on the basis of a single, high serum CEA result alone.

There were 29 patients with evidence of hepatic metastases by clinical examination supported by abdominal ultrasonography, abdominal CT scanning or operative findings. Twenty seven of these patients had a serum CEA of ≥100 u/l and 23 had a serum CEA of ≥ 160 u/l. The results for sensitivity, specificity, PPV, NPV, and accuracy have been calculated for the detection of recurrence and specifically for the detection of hepatic metastases for serum

CEA at both 100 u/l and 160 u/l. In order to compare the significance of the two levels of serum CEA in determining recurrence, χ^2 values have been calculated and compared (*Table 6*).

	Recurrence			**Hepatic recurrence**		
	60 u/l	100 u/l	160 u/l	60 u/l	100 u/l	160 u/l
Sensitivity	89	87	64	93	93	85
Specificity	82	89	92	65	72	83
PPV	79	85	85	44	50	57
NPV	91	90	78	97	97	95
Accuracy	85	88	80	77	77	83
χ^2	64.2	71.26	43.71	42.16	38.3	44.7

Table 6. The accuracy of serum CEA estimation in determining the presence of recurrent disease and the presence of hepatic metastases in patients in routine follow-up after curative resection of colorectal cancer. The value of χ^2 has been calculated for each column from the values of TP, TN, FP, FN. (see Fig 13.) The higher the value of Chi sq, the more likely it is that patients have been divided into those with and those without recurrence on the basis of the serum CEA value. All of these results reach significance at $p < 0.001$ level.

VII.E. Discussion

Serum CEA elevation may be related to a number of primary pathologies (Kalvins JV, 1985). Elevation of serum CEA, in conjunction with suspicious lesions on either barium enema examination or colonoscopy, supports the diagnosis of colonic malignancy. A rise in serum CEA may be related to the presence of local recurrence or hepatic metastases (Finlay IG, 1983; Sugarbaker PH, 1976; Wood CB, 1980) in patients who have undergone resection of a primary colorectal cancer. In group 1, 78% of patients had elevation of serum CEA above 60 u/l associated with the presence of hepatic metastases. Twenty two percent of the colon cancers in this group did not produce CEA. It has been shown by others (Mackay AM, 1974; Minton JP, 1985) that around 20% of colorectal recurrence do not produce an elevation of serum CEA. Sixty eight percent of patients with hepatic metastases had a serum CEA of > 160u/l. Elevation of serum CEA was loosely related to volume of liver involved by metastases. This suggests that the larger the

volume of metastases the greater the serum CEA for those cancers which produce CEA. The level of serum CEA at the time of staging was significantly higher in patients with irresectable disease ($p<0.05$ Mann-Whitney test corrected for paired results), although the range of values for serum CEA was so wide that the two groups overlapped entirely. This data confirms that elevation of serum CEA is an indicator of recurrent disease but is too inaccurate (accuracy of 58% for serum CEA $\geq$ 1000 u/l) to indicate irresectable, recurrent hepatic disease. Elevation of CEA may be caused be other tumour burden apart from that in the liver. Although this would also be an indication that the patient was not suitable for resection.

At presentation, 44% of patients (in group 2) with a diagnosis of colon cancer had a serum CEA level of > 60 u/l. This is fewer patients than expected and at the lower end of the reported range (Sikorska H, 1988). Group 2 represents a selected group of patients who had undergone an IOUSS. There are fewer stage D cancers than expected (Hardcastle JD, 1986) in group 2, this may be explained by some unrecognised selection of patients prior to operation. It is possible the GPs referring patients with advanced disease may have had a preference for the Western General Hospital (WGH)(not included in this part of the study), as the regional oncology centre is on that site. This is supported by a higher than expected number of Dukes 'D' patients in group 3 which was drawn from the WGH.

Very high levels of serum CEA are an indication of poor prognosis (NIH Consensus statement 1981) and so serum CEA may be used as an adjunct to pathological staging (CEA and prognosis is explored in a subsequent chapter). There was a significant relationship between elevation of serum CEA and the presence of hepatic metastases. The median for patients with no metastases was 48 u/l compared to 91 u/l for those with metastases ($p < 0.05$ Mann-Whitney U test). Dividing the group at a CEA level of 160 u/l gave the most significant difference, in the groups of patients with a χ^2 value of 9.77. Previous studies have also noted the relationship between CEA and hepatic metastases (Finlay IG, 1983; Herrera MA, 1976; Sugarbaker PH, 1976). However, the upper limit of normal in these studies was 25 μg/l or 250 u/l using our standard, which is much higher than our upper limit of normal (60 u/l). Elevation of CEA was related to the presence of recurrence and to poor prognosis in all of these studies.

During the follow up period, we were unable to show that the appearance of metastases on IOE scanning preceded elevation of serum CEA or vice versa.

The two events were coincident in those patients whose cancers produced CEA. This was to be expected, as the serum CEA estimations were made at the same time as the IOE scans and were used to confirm the findings of the scans . It has been suggested that serum CEA estimations must be made with a much higher frequency (monthly) to provide early detection of recurrent disease (Martin EW, 1977; Sugarbaker PH, 1976). Finlay has suggested that serum CEA elevation lags behind detection of hepatic metastases by CT scanning (Finlay IG, 1983). Again the upper limit of normal for CEA in Finlay's study was 250 u/l, more than four times the upper limit of normal in our laboratory and 90 u/l higher than the most accurate level for the detection of metastases in our series. It is impossible to say from these data that the elevation of serum CEA in patients in group 1 preceded the presence of detectable recurrent disease, as this data was not recorded. Patients in group 3 had regular out-patient follow-up and estimation of serum CEA at each clinic visit. Serum CEA elevation preceded clinical evidence of disease in 38 (72%) of 53 patients with recurrence undergoing classical out-patients' review. This is similar to previously reported series (Mackay AM, 1974; Mach JP, 1978)

The data from group 2 show that palpation at operation had an accuracy of 81%, and 97% when combined with IOUSS in the detection of hepatic metastases. A serum CEA of ≥ 160 u/l indicated hepatic involvement in 23% of patients with 71% accuracy and a level of 100 u/l indicated involvement in 28% of patients with 67% accuracy. This compares favourably to preoperative ultrasonography which indicated hepatic metastases in 21% of patients with an accuracy of 69%. In patients being followed-up after resection of colorectal cancers, a single serum CEA estimation of ≥100 u/l indicated recurrent disease with a positive predictive value (PPV) of 85% in 43% of the population and a value of 160 u/l will indicate hepatic recurrence with a PPV of 57% in 32% of the population. It is not possible to compare the accuracy of IOE scanning and serum CEA estimation in the detection of hepatic metastases from these data as the results of one of the investigations were used to confirm the finding of the other.

These data show a significant relationship between serum CEA and the presence of colorectal cancer metastases (group 1). They also show a significant relationship between elevation of serum CEA above 160u/l and the presence of hepatic metastases at the time of presentation with colorectal cancer (group 2) which is independent of Dukes stage. Elevation of serum CEA in the follow-up period was significantly related to the presence of recurrent disease overall

and at a higher level to the presence of hepatic metastases (group 3). The level of CEA of ≥160 u/l was found to be the most significant in determining the presence of hepatic metastases at the time of primary resection and during follow up. There were no data collected from the patients in group 3 to define which patients found to have hepatic metastases following a serum CEA rise to 160 u/l then went on to successful hepatic resection. From group 1, successful hepatic resection was significantly related to levels of serum CEA< 1000 u/l.

Two of the major advantages of serum CEA testing is that it is cheap, and easily repeatable. These data shows that serum CEA estimation is more accurate than clinical examination in determining which patients have recurrent disease. These data have not clarified the temporal relationship of serum CEA elevation and appearance of metastases on plain CT scan or abdominal ultrasound. However, data from Group 1 suggests a relationship between lower levels of serum CEA and fewer hepatic segments being involved by tumour and data from Group 2 suggests that serum CEA increases with time in patients with hepatic metastases. Detection of serum CEA elevation of ≥160 u/l will indicate patients who have hepatic recurrence with 83% accuracy in the follow up period. If the serum CEA elevation is below 1000 u/l the hepatic recurrence is more likely to be resectable. We have shown (chapter V) that patients will not accept repeated IOE scans as a form of follow up for their colorectal cancer. No studies to date report the use of enhanced CT scanning in the routine follow up of patients with colorectal cancer, outwith prospective clinical trials. Repeated CEA estimation is a realistic adjunct to clinical follow up which is inexpensive and non-invasive. Its lack of accuracy is more than compensated for by it availability and ease of use. This study has confirmed the clinical value of CEA as a marker of recurrence and the presence of hepatic metastases following curative resection of colorectal cancer.

Chapter VIII

Initial development and use of laparoscopic ultrasonography in the detection of hepatic metastases

VIII.A. Introduction

Chapters V and VI have shown as have others that IOUSS is the most accurate method of detecting metastases at the time of operation (Machi J, 1987; 1991; Boldirini G, 1987; Bismuth H, 1987; Makucchi M, 1987; Sheu J-C, 1985; Olsen AK, 1990; Clarke MP, 1989; Gozzetti G, 1986; Charnley RM, 1991). The major drawback of the technique is the need for laparotomy. Recent advances in the field of laparoscopy have led to a resurgence of its use by the surgeon. Laparoscopic staging of malignant disease is not new but has always been limited to a visual assessment and biopsy (Cuschieri A, 1978; Warshaw AC, 1990). As examination of the liver is limited to the surface of the organ, the internal mass cannot be examined (Watt I, 1989). Previous development of laparoscopic ultrasonography was limited by the technical performance of small transducers but in particular the lack of a suitable linear array which could be passed through a laparoscope port (Okita K, 1984). Confirmation of the accuracy of IOUSS in the detection of hepatic metastases and a recognition of the limitations of pre-operative investigations, including IOE scanning, in the accurate assessment of patients prior to laparotomy for resection of hepatic metastases has led to the development of laparoscopic ultrasonography. Expertise gained in the field of IOUSS has led to successful outcome for a pilot study. Further development of laparoscopic surgery and in particular surgery for colorectal cancer may require surgeons to perform laparoscopic examination of the liver as a matter of routine at the time of laparoscopic resection.

VIII.B. Aim

To develop a practical method of performing contact ultrasonography of the liver by laparoscopic access to the abdominal cavity. To perform a pilot, feasibility study, using this technique and compare its performance to IOUSS and IOE scanning in the detection of known hepatic metastases.

VIII.C. Patients and methods

There were 147 patients who were being assessed for resection of known hepatic metastases (discussed in chapter III). Of these, 23 gave informed consent to laparoscopy and laparoscopic ultrasonography, prior to laparotomy and IOUSS. The equipment to perform laparoscopic ultrasonography was available from April 1991. Patients were not suitable for laparoscopic ultrasonography if it was not possible to perform laparoscopy for any reason. Patients had already undergone CXR, preoperative USS and IOE scanning of the liver. A number of patients had also had CT scans of the chest. In the initial series all patients were planned to go on to laparotomy.

VIII.C.1. Equipment.

There were no commercially available laparoscopic ultrasound probes at the inception of this study. There were, however, linear array 5 and 7.5 MHz endo-anal probes. These are used for the imaging and accurate biopsy of prostate cancer and mapping of anal sphincters prior to anal canal surgery. The Aloka endo-anal ultrasound probe has both a suitable scanning array and a long enough shaft to allow access to the abdominal cavity. The probe has an external diameter of 18 mm and is too large to fit down an ordinary laparoscope port. WFAM designed and built a custom port with the help of a local medical engineering company (Oxyliter, Edinburgh). The design criteria were that the port could replace an ordinary laparoscope port without loss of pneumoperitoneum, allow the endo-anal ultrasound probe to be inserted and manipulated without damage to the patient or the probe and that at the end of the procedure the large port could be used to pass an ordinary 10 mm laparoscope. All of these criterion were met by the first design (*Plate 1*). The large bore laparoscope port consisted of four main parts: an obturator rod, a dilator, the port, and a downsizer. The port and the downsizer both contained replaceable silastic seals to maintain pneumoperitoneum. The entire device was constructed from surgical steel and medical grade silastic.

The probe was connected to the Aloka 610 echo camera; the images obtained were stored on video tape and as still prints.

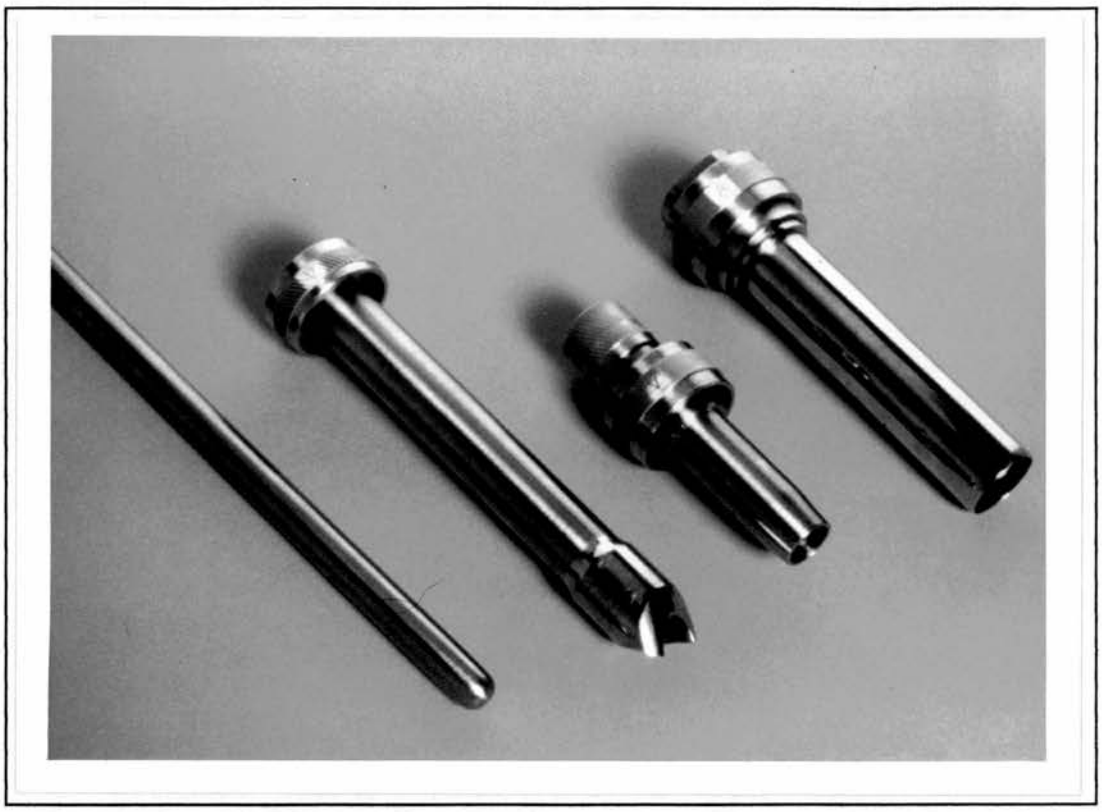

Plate 1. The large bore port assembly with obturator, dilator, large bore port, and downsizer. The entire assembly was constructed using an original design from surgical steel and medical grade silastic.

VIII.C.2. Operation

Pneumoperitoneum is obtained by Veress needle puncture in the supra-umbilical position to an intra-abdominal pressure of 14 cm of water. A 10 mm disposable laparoscope port is introduced in the supra umbilical position and routine laparoscopy performed. A second 10 mm port is introduced in the epigastric position and the laparoscope transferred to this position. The obturator rod of the large port is introduced through the epigastric port and the port removed, leaving the rod in place. The large port and dilator assembly is placed over the rod and pushed into the abdominal cavity under direct vision. The dilator and rod are removed and the endo anal probe inserted through the large port.

VIII.C.3. Scanning

The crystal array is manipulated onto the upper surface of the liver under direct vision. The scan of the liver can then take place. Because of the altered

orientation of the scanning probe to the liver and the limitations of movement of the probe, the actual examination technique is quite different to that performed at open operation.

VIII.C.4. Position 1

With the probe head lying immediately to the right of the falciform ligament, and with the proximal edge of the scanning face at the inferior border of the liver and the scanning face pointing in a posterior direction, the probe is gently and slowly rotated in a clockwise and anti-clockwise direction through and arc of 5-10°. Whilst the probe is being slowly rotated it is advanced, both the primary divisions of the intrahepatic portal vein and the origin of the hepatic veins are seen (*Fig 1*). This is the basic starting point of the scan and the point of reference when defining the intra-hepatic anatomy. The probe is then advanced over the anterior surface of the liver to its maximum extent.

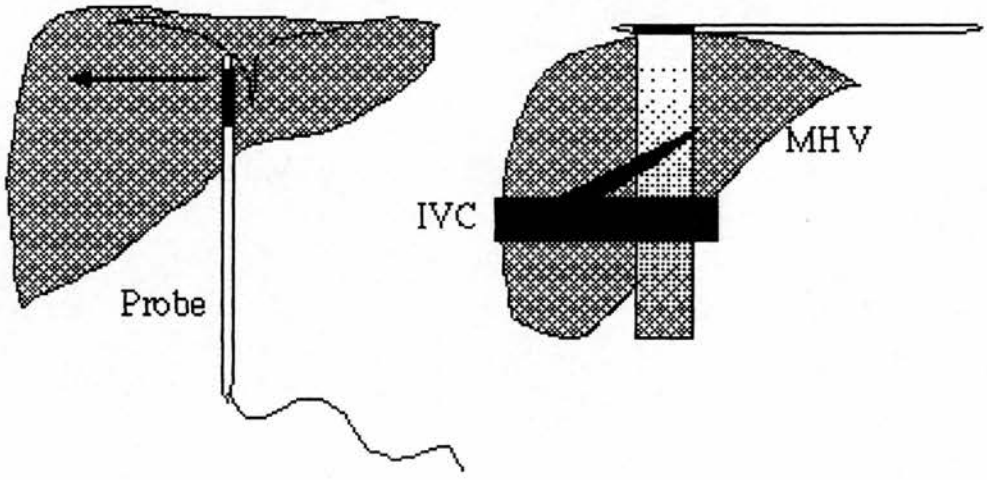

Fig 1 Position 1 The probe is advanced until both the primary confluence of the portal vein and the origin of the hepatic veins have been seen.

VIII.C.5. Position 2

At the start of each scan, the most superior part of the liver is viewed. By advancing the probe until either the head of the probe loses contact with the surface of the liver, because of its natural curve, or the tip of the probe is pushed hard up against the under surface of the diaphragm, the most superior part of the vena cava can be viewed. By sweeping the probe to the right and

pushing in; the sub diaphragmatic part of the right lobe of the liver is demonstrated (*Fig 2* .).

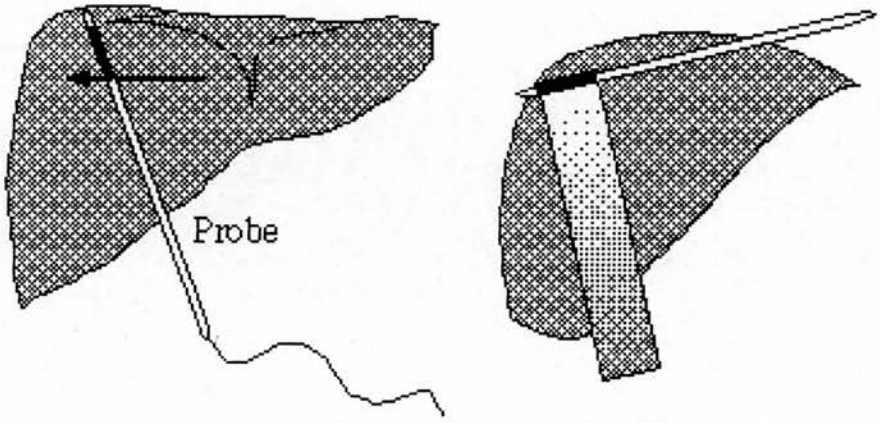

Fig 2. Multiple sweeps of the right lobe of the liver are made pushing the probe in and sweeping to the right . Small rotatory movements of the probe are made as it is swept slowly to the right.

Once this has been done the probe is returned to position 2 and swept in an arc to the right across the right lobe of the liver. This is repeated in successive arcs across the surface of the liver with, on each occasion, the probe starting a little nearer to the inferior border of the liver. The lateral extent of each scan is the point at which either the under surface of the liver is encountered or the face of the probe loses contact with the surface of the liver because of its natural curvature. The right lobe having been scanned, the left lobe is dealt with in a similar manner.

VIII.C.6. Position 3

With the probe lying to the left of the falciform ligament, the tip is swept to the left and pushed in. This demonstrates the most superior part of the left lobe. Successive sweeps across the left lobe are then made until the entire lobe has been visualised.

VIII.C.7. Interrogation

At open intraoperative ultrasonography, small movements of the fingers are used to gently tilt the scanning head through a few degrees of an arc. This causes the plane of the scan to pass through the region of interest over and over again. The same effect can be obtained with the laparoscopic probe by gently

rolling the probe between the fingers of the examining hand causing the shaft to rotate by a few degrees. This small movement causes the plane of the scan to sweep back and forth through the area of interest giving an impression of three dimensions (*Fig 3*).

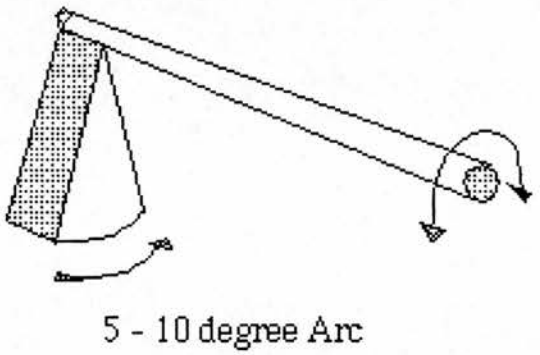

Fig 3 By making small rotational movements of the shaft of the probe regions of interest can be viewed again and again giving the impression of three dimensions.

VIII.C.8. Biopsy

Once a lesion has been identified, it is possible to biopsy it under ultrasound control by inserting a 'Tru-cut' biopsy needle through the anterior abdominal wall and into the surface of the liver. The biopsy needle is prepared by scratching its tip to improve its echo signal. The tip of the needle can then be placed directly into the lesion to be biopsied under ultrasonic control and the sample obtained. Biopsy of surface lesions are obtained by using forceps inserted through a separate 5 mm port in the infra-costal area.

VIII.D. Results.

All 23 patients had IOE scans which suggested resectable hepatic metastases, 2 went on to successful resection of their hepatic metastases following laparoscopic ultrasonography. Of the remaining 21 patients, 2 had no evidence of any malignant disease. Eleven patients had widespread intra-

abdominal disease on laparoscopy; 2 of these also had irresectable multiple hepatic metastases. In 7 patients, laparoscopic ultrasonography revealed widespread intrahepatic disease not seen on IOE scanning. In one of these patients tumour thrombus from a hepatoma was identified in the left portal vein (Plate 2).

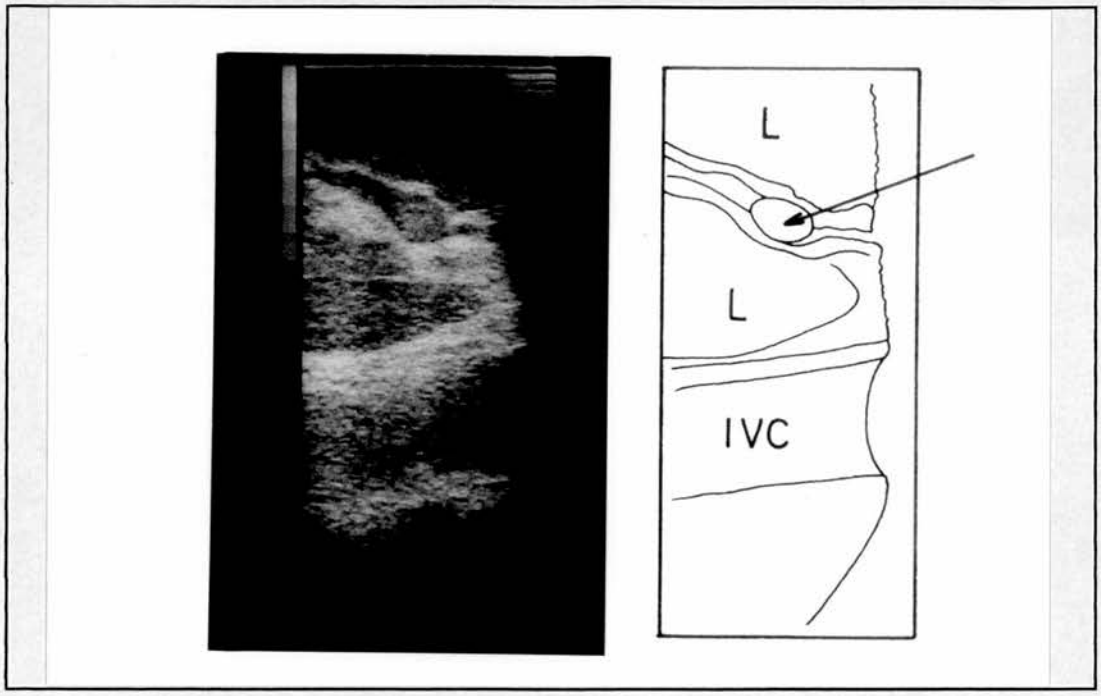

Plate 2 Tumour thrombus in the left portal vein on Laparoscopic ultrasonography.

In one patient laparoscopy was impossible because of adhesions. There were no complications related to the investigation and there were no equipment failures.

VIII.E. Discussion

The use of laparoscopy as a staging investigation is not new, (Cuschieri A, 1978; Watt I, 1989; Warshaw AC, 1990; Cuesta MA, 1992) but its use in malignancy of the liver has been restricted by the inability to "see" into the solid organ. This limitation is removed by laparoscopic ultrasonography. Previous attempts at laparoscopic ultrasonography have failed because of the technical limitations of the small array probes used (Ohta Y, 1981: Oda M, 1982; Okita K, 1984) . These limitations have now been removed (Asher SM, 1992; Murugiah M, 1993; Windsor JA, 1993).

This series is not randomised and represents patients in whom the feasibility and general performance of the technique of laparoscopic ultrasonography has been assessed. Indirect comparison may be made to the group of patients considered chapter IV from which this subgroup of patients was drawn. The successful resection rate was much higher (66%) in patients who had open staging than those who were staged laparoscopy and laparoscopic ultrasonography (8%). Patients with irresectable intra-hepatic disease made up 69% of the inoperable cases in the open group and only 38% of the inoperable cases in the laparoscopy group. All 23 patients in the laparoscopy group would have had a staging laparotomy including intraoperative ultrasonography before resection of their liver metastases had they not undergone laparoscopy. It is worthy of note that both patients who had resectable disease defined by laparoscopic staging went on to successful resection where as 13% of the patients who went directly to laparotomy had irresectable disease.

These data suggest that laparoscopic ultrasonography may obviate the need for IOE scanning prior to laparotomy and hepatic mobilisation. What then is the role of IOE scanning in these patients? In the patients discussed in chapter IV the IOE scan was used to identify those with potentially resectable metastases. All of the data from chapter IV, V and VI suggest that contact hepatic ultrasonography is more accurate than IOE scanning in the detection of intrahepatic malignancy at the time of operation. The data in this series shows that laparoscopy can detect the peritoneal spread of disease, which IOE scanning cannot, and that laparoscopic ultrasonography is more sensitive that IOE scanning in the detection of intrahepatic disease. A rationalisation of the pre-operative staging of patients with hepatic malignancy would suggest the following investigations; preoperative chest Xray or thoracic CT scan, pre-operative USS of the abdomen and serum CEA to exclude gross disease. Patients who have had colorectal malignancy should undergo visualisation of their remaining colon prior to laparoscopy. These patients should then have laparoscopy and laparoscopic ultrasonography as the staging investigation of choice and should only go on to IOE scanning or another form of enhanced CT scan if the results of the laparoscopic investigations are in any way ambiguous or laparoscopy is not possible.

These results are very encouraging and suggest laparoscopic ultrasonography is an important technique in the assessment of patients prior to resection of hepatic malignancy. Laparoscopic ultrasonography can significantly reduce the number of patients undergoing negative staging laparotomy for hepatic

malignancy and so reduce both the length of hospital stay and morbidity in these patients.

Laparoscopic colectomy is now a practical procedure (Schlinkert RT, 1991; Wexner SD, 1992; Monson JR, 1993) and has been performed in patients with both benign and malignant disease (Fugger R, 1993). Initial fears that it may be impossible to perform a radical cancer operation, with a satisfactory lymph node harvest appear to be unfounded (Falk PM, 1993). It is however clear that it is impossible for the surgeon to palpate the liver during laparoscopic colon resection. Laparoscopic ultrasonography provides a means whereby the disadvantage of being unable to perform hepatic palpation can be negated. There is no doubt that examination of the liver is an important part of the laparotomy for colorectal cancer, laparoscopic ultrasonography allows the laparoscopic surgeon to examine the liver with as much if not more accuracy than a surgeon, at open operation, performing palpation alone.

It is likely that in the future laparoscopic ultrasonography will become a standard investigation performed at staging laparoscopy for patients prior to resectional surgery for intra-abdominal malignancy. Commercial interest has boomed since 1991, with a number of companies now producing sophisticated laparoscopic ultrasound probes which incorporate colour Doppler imaging within variable frequency, variable focus linear array scanning heads. This type of equipment will greatly enhance the development of laparoscopic ultrasonography.

Chapter IX

Survival analysis

IX.A. Introduction

In chapter I, the importance of staging in the treatment of colorectal cancer was discussed. Staging systems have been developed by relating known outcome to factors which can be assessed at presentation and operation for colorectal cancer. In this chapter, the presence of a number of factors are related to the survival of a group of patients with colorectal cancer.

All of the patient who had IOUSS performed at the time of curative colorectal surgery have been followed up for a minimum of 2 years. Patients who agreed to IOE scanning in the follow up period have had extensive investigation, those who refused have been followed up via their general practitioners. Details of survival or the date of death have been collected for all patients.

IX.A.1. Aim

This chapter correlates survival to the presence of risk factors detectable at the time of presentation with colorectal cancer. The aim is to find which factors have independent prognostic significance and which do not. This information can then be used to suggest a rational protocol of investigation at the time of primary resection for colorectal cancer.

IX.A.2. Method

The follow up and details including date of death are contained in the colorectal cancer database. The database has been used to link known outcome to potential risk factors. Patients have been grouped according to these factors into a new database entitled SURVIVAL.dbf (Appendix 3).

IX.A.2.a. Patients

Patients from the colorectal cancer database are discussed (Chapter VI); all patients who had, undergone an intraoperative ultrasound scan and in whom the diagnosis of colorectal cancer had been confirmed were included in this analysis (147 patients). These patients have been discussed in chapter VI.

IX.A.2.b. Life table calculation

Life table calculations have been carried out with the assistance of the Department of Medical Statistics (RAE) using SPSS. Cox proportional hazards regression was used to test the association between factors recorded at the time of operation and subsequent mortality. Each factor was tested separately (univariate analysis), and then a forward stepwise procedure was used to identify factors that gave independent prognosis.

IX.A.3. Results

Life tables were calculated for the following: Dukes stage A, B and C, the presence of hepatic metastases, the presence of a preoperative CEA of ≥160 u/l, the presence or absence of weight loss and the grade of surgeon performing the primary colorectal resection. The longest follow up was for 50 months median 39 months range 24 to 50 months. Seventy patients died (48%) during this time. Thirty eight men and 32 women died, representing 48% and 42% of the populations of each sex respectively

IX.A.3.a. Cox proportional hazards regression analysis

Univariate and multivariate analysis were used. The multivariate analysis was calculated for all patients (n = 147) and for patients who in whom the primary cancer had been assigned a Dukes stage (n = 121) (Table 1).

Factor	Significance		
	Univariate	Multivariate 1	Multivariate 2
Age at diagnosis	NS	$p < 0.05$	$p < 0.01$
CEA≥160	$p < 0.001$	$p < 0.001$	$p < 0.05$
Cure	$p < 0.01$	NS	NS
IOUSS mets	$p < 0.001$	$p < 0.001$	$p < 0.001$
Grade of surgeon	$p < 0.05$	$p < 0.05$	$p < 0.05$
Weight loss	NS	NS	NS
Dukes stage	$p < 0.001$	-	$p < 0.001$

Table 1. Cox proportional hazards regression of 7 prognostic factors for patients having primary resection of colorectal cancers. Multivariate analysis 1 includes all patients (n = 147) and excludes Dukes stage from the calculation. Multivariate 2 includes the Dukes stage in the calculation and excludes the 26 patients for whom there was no Dukes stage.

IX.A.3.b. Life tables

These have been calculated and drawn by SPSS (RAE) and are presented on the following pages.

IX.A.3.c. Survival by dukes stage.

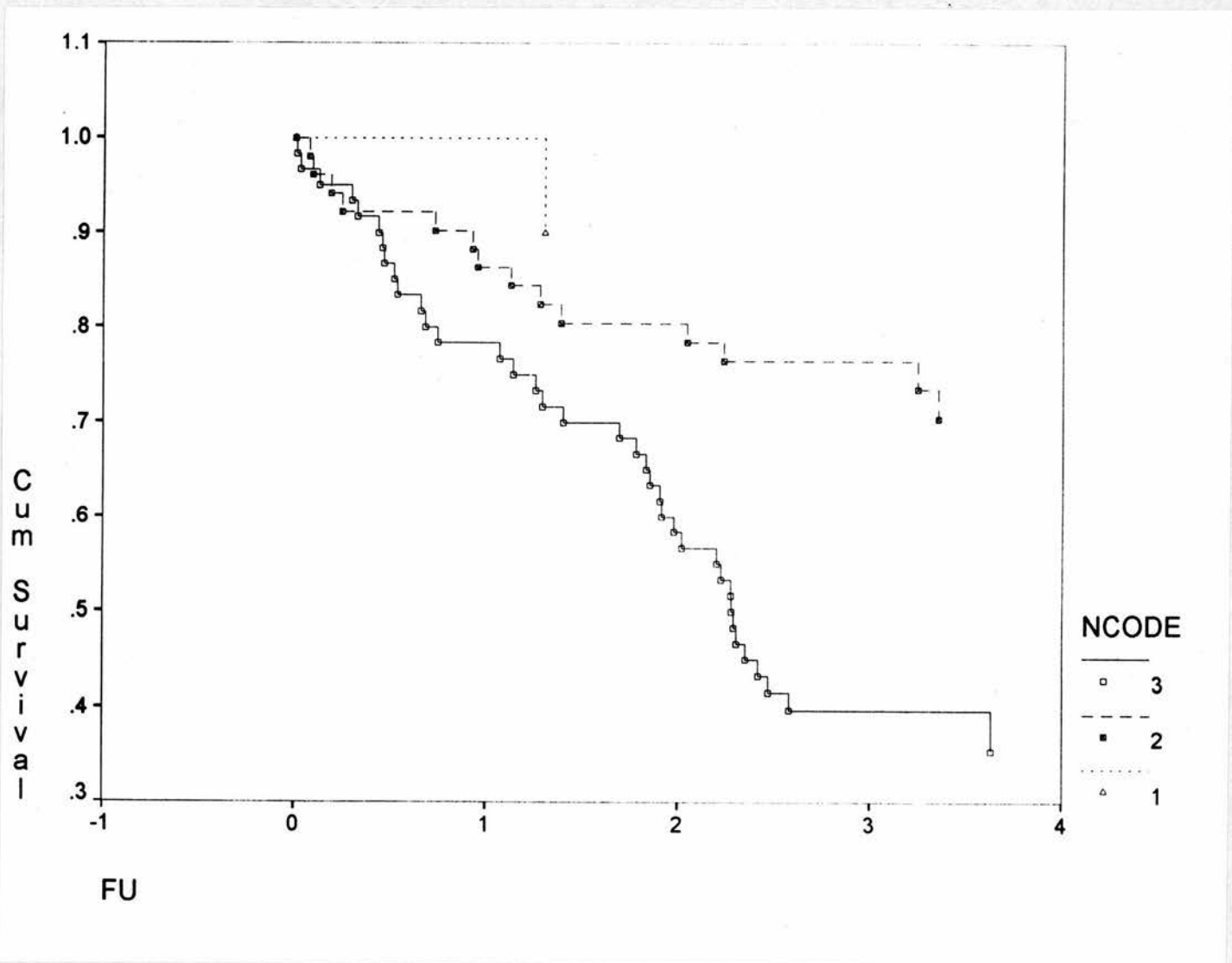

Fig 1 Life table for survival related to Dukes stage at presentation. There were 121 patients in whom the Dukes stage of disease was known. Of these there were 10 Dukes 'A', 51 Dukes 'B' 59 Dukes 'C' and 1 Dukes 'D'. Dukes C and D have been grouped together. FU = follow up in years. NCODE 1 = Dukes A, 2 = Dukes B, 3 = Dukes C and D.

IX.A.3.d. Survival by surgical "cure"

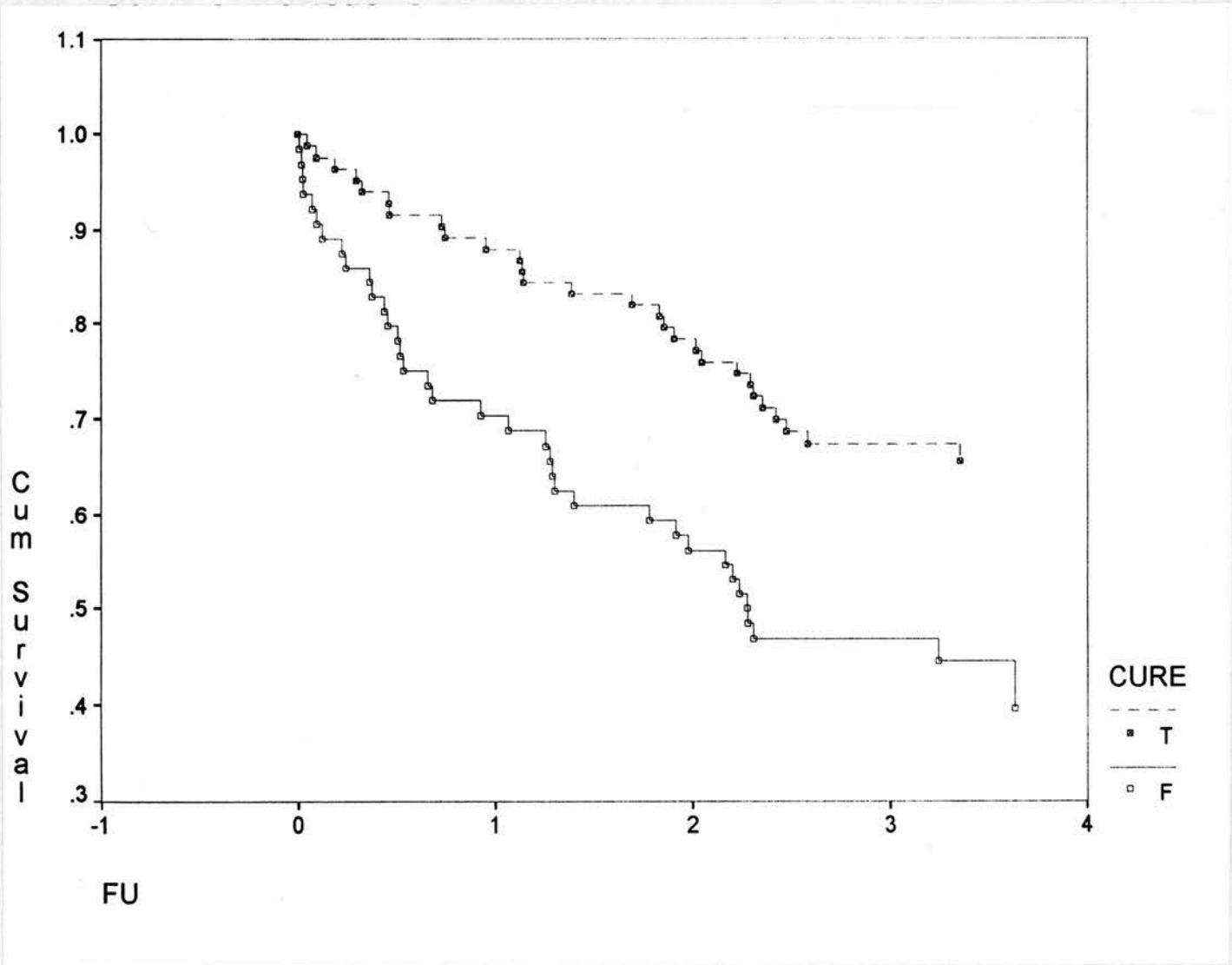

Fig 2 Life table of survival for patients in whom the surgeon thought he had performed a curative resection and those in whom he felt he had not. FU = follow up in years. CURE = T, those patients who had a curative resection. and F, those who did not. Patients in whom the surgeon thought he could palpate metastases are in the F group whether or not they actually had metastases.

IX.A.3.e. Survival by serum CEA ≥ 160 u/l

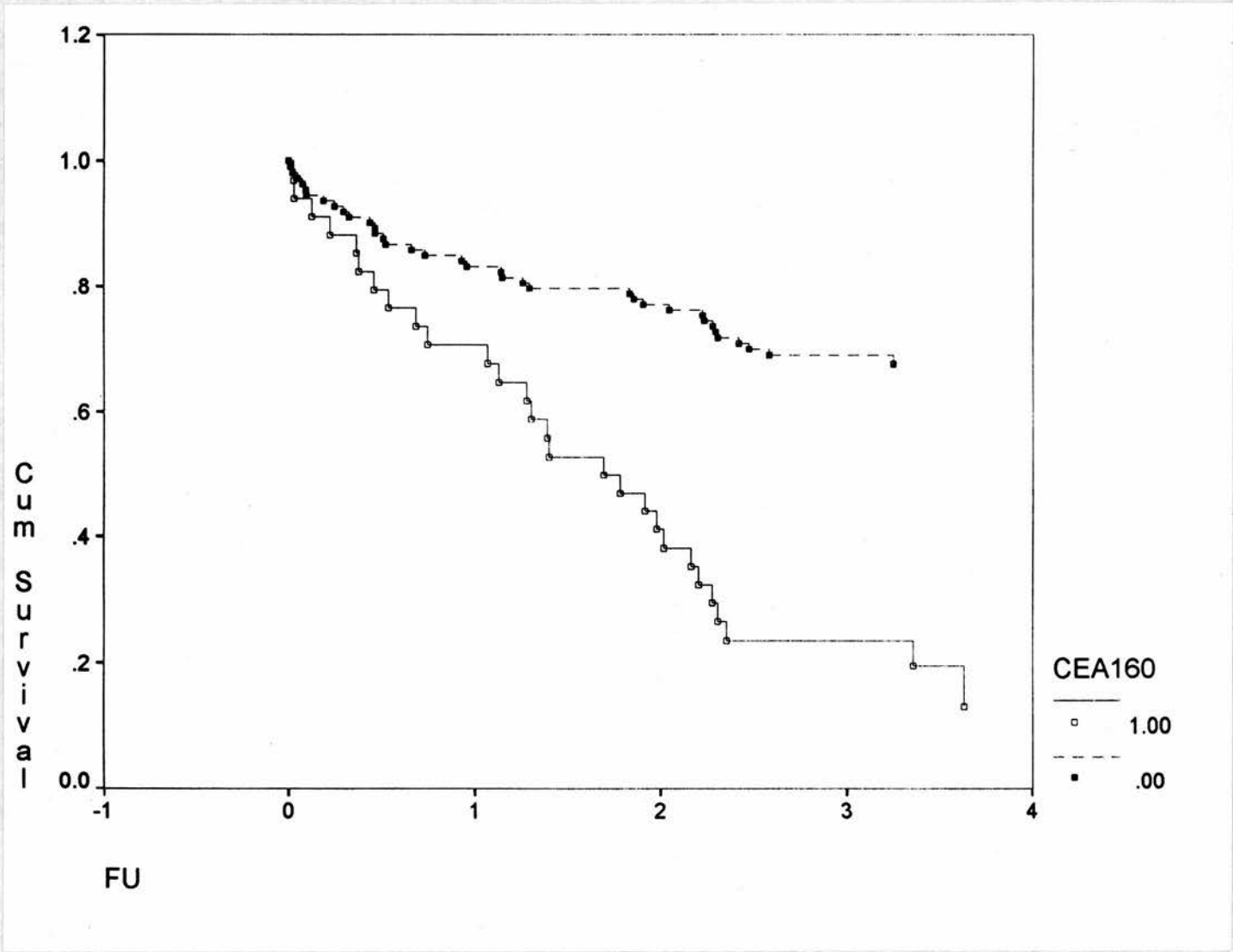

Fig 3. Life table for patients in whom the serum CEA at presentation was ≥160 u/l and those in whom it was not. CEA160 (1.00) = CEA ≥160 u/l , CEA160 (.00) = CEA < 160 u/l. FU = Follow up in years.

IX.A.3.f. Survival by the presence of metastases at operation by IOUSS

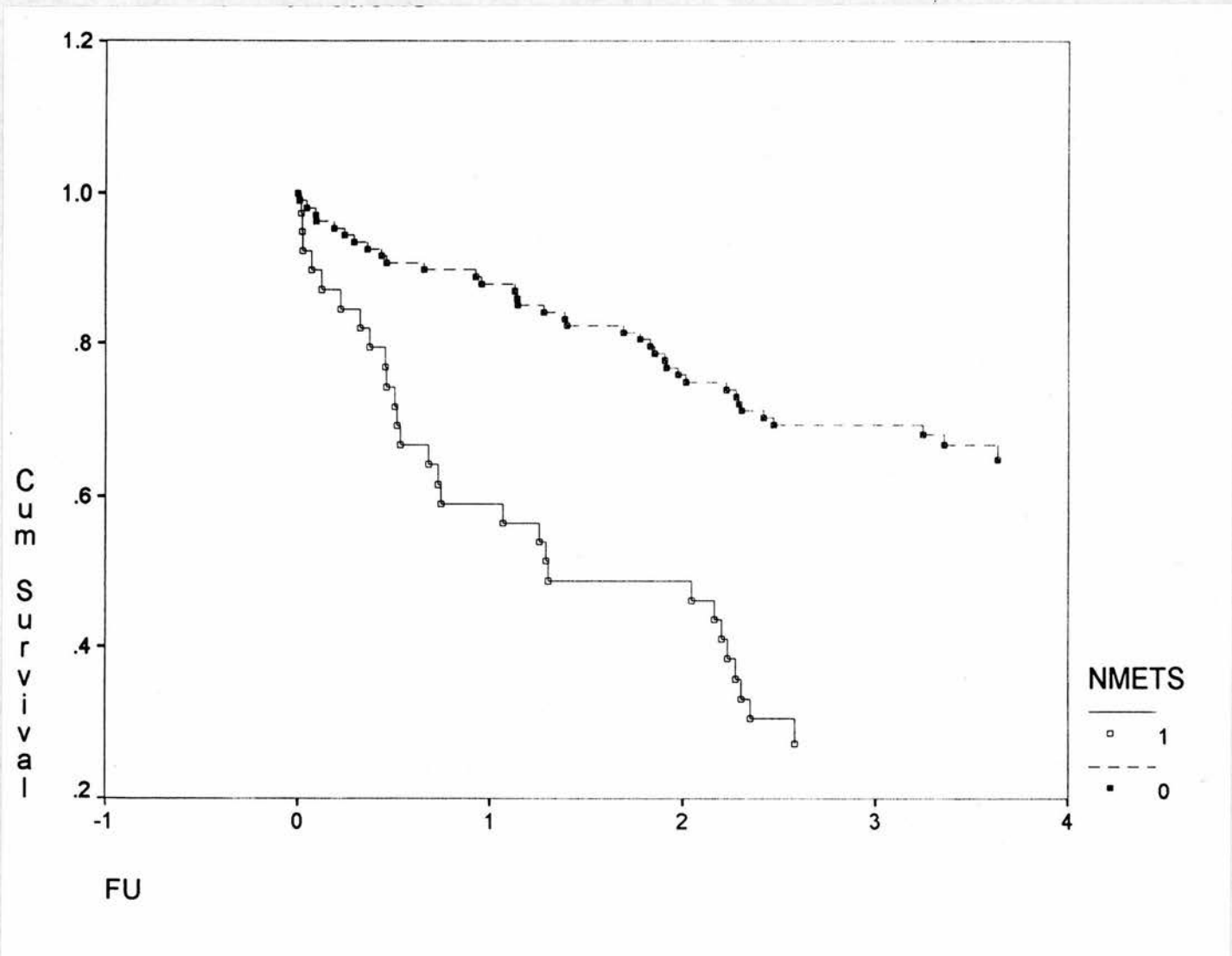

Fig 4. Life table of survival by the presence/absence of metastases by IOUSS at operation. NMET 1= metastases present on IOUSS. NMET 2 = no metastases present on IOUSS. FU = Follow up in years.

IX.A.3.g. Survival by grade of the principle surgeon performing the operation

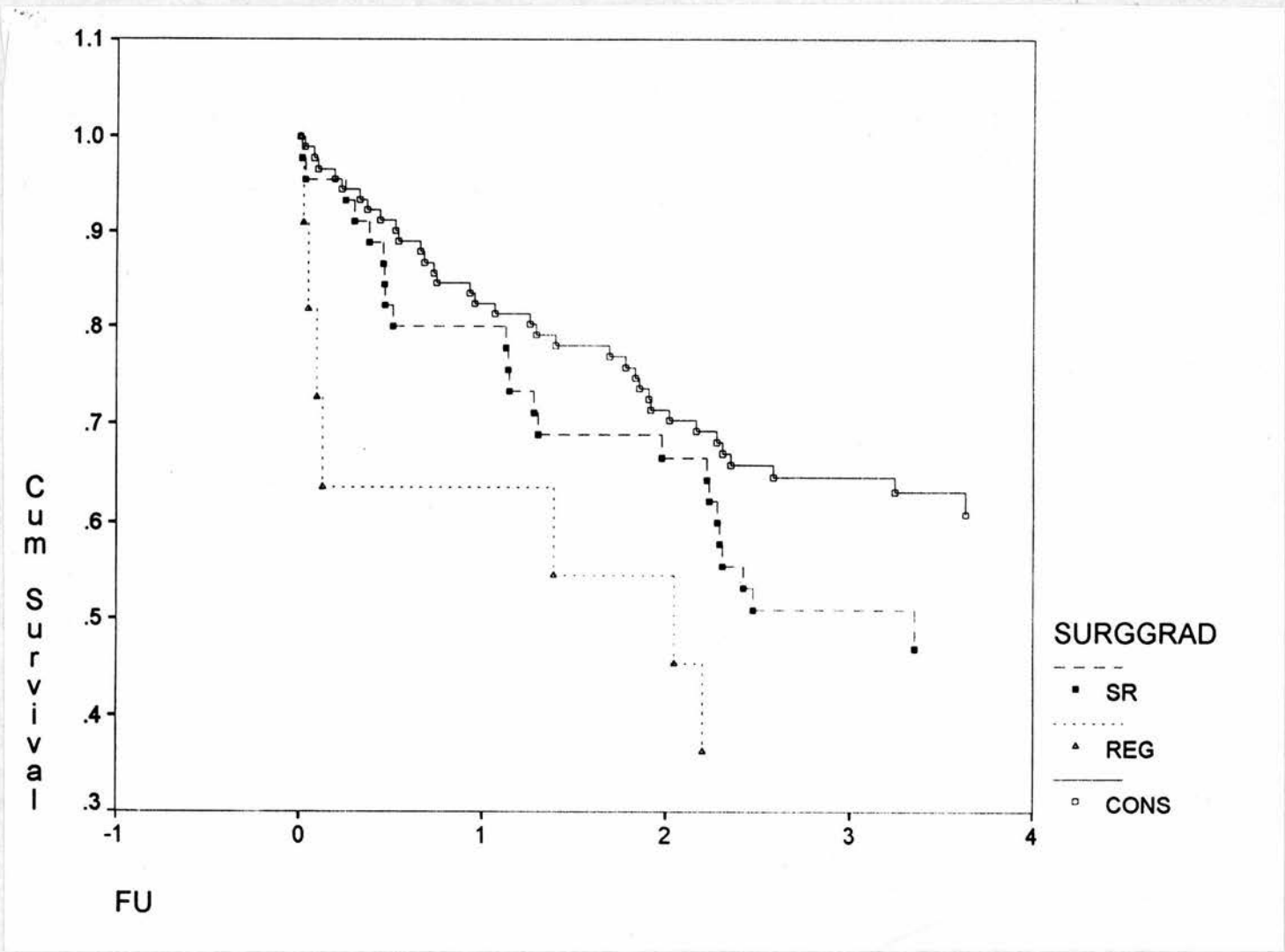

Fig 5. Survival by the grade of principle surgeon performing the primary surgery. SURGGRAD; CONS = Consultant, SR. = Senior Registrar, REG. = Registrar. FU = follow up in years.

IX.B. Discussion

Both the univariate analysis and plots of the life tables (*Fig 1-5*) have shown that the Dukes stage, the presence of metastases at operation by IOUSS, elevation of serum CEA to ≥160u/l, the grade of surgeon performing the operation and whether or not the surgeon felt he had performed a curative resection are significantly related to survival (Table 1). The forward stepwise procedure has identified which of these factors are independent variables. This analysis has been performed on two groups of patients: those in whom the Dukes stage was known and the whole group independent of Dukes stage. This shows that; age at diagnosis, CEA at presentation of ≥ 160u/l, the presence of metastases detected by IOUSS, the grade of the surgeon performing the operation and the Dukes stage of the primary tumour all have independent significance. These, then, are the factors that should be assessed at the time of resection in order to more accurately predict the outcome for any individual patient.

Duke and others have shown that the primary tumour's local, vascular and lymphatic spread is an indicator of prognosis and also that metastatic spread outside the field of resection is a negative factor. (Miles EW, 1925; Michelassi F, 1991; Murray D, 1975; Dukes CE, 1932; 1958: Jass JR, 1987; Rankin FW, 1928; Brown CE, 1938; Sunderland DA, 1949; Collier FA, 1940). The site and presentation of the cancer in the colon or rectum had been given significance (Jeekel J, 1987), as had its genetic makeup, in particular the presence or absence of tumour related genes (Monnat M, 1987).

In this series, both the Dukes stage and the presence or absence of metastases on IOUSS are powerful independent prognostic indicators. Dukes staging has been discussed in chapter I. It is the most commonly used staging classification in Great Britain and widely quoted in the literature. The prognostic importance of occult metastases detected during follow up has been described by Finlay (1983). The ability to detect these small metastases at the time of surgery by IOUSS has been described (Charnley RM, 1991; Machi J, 1991; Clarke MP, 1989: Boldirini G, 1987; Olsen AK, 1990; Soyer P, 1992; Stewart PJ, 1993; Knol JA, 1993; Boutkan H, 1991) however the independent prognostic significance of metastases detected by IOUSS at the time of primary surgery has not been reported. As previously

reported by Finlay, the presence of impalpable metastases is independent of Dukes stage.

Although elevation of CEA has a significant relationship to the presence of metastases (Wanebo HJ, 1978; 1981; 1994; Minton JP, 1985; Herrera MA, 1976; Norton JA 1991; Sikorska H, 1988; Schneebaum S, 1993; Seregani E, 1994), it also remains an independent prognostic indicator on multivariate analysis. This suggests, as would be expected, that CEA is an indicator of the presence of disease in general and not just of hepatic metastases. That elevation of CEA is related to the presence of hepatic metastases reflects that the liver is the most common site of metastasis for colorectal cancer.

In this series, the seniority of the surgeon who performed the primary operation was a significant predictor of outcome on univariate analysis. This might have been expected if there was case selection of patients more complex or difficult case were operated on by the more senior surgeon. However the significance of grade of surgeon remains in both groups of multivariate analysis. This is an unexpected finding as the operations performed by juniors are supervised and controlled by their seniors. Such a profound difference in outcome related to the grade of surgeon performing the operation has not been previously reported.

The age of the patients at diagnosis is not of prognostic significance on univariate analysis. However, on multivariate analysis it becomes a significant independent factor and, as expected, the older patients have a poorer outcome than younger patients.

IX.C. Conclusion

Current clinical practice in Edinburgh is for the operating surgeon to make an assessment, at operation, as to whether the operation has achieved a curative resection. The resected specimen is then examined by the pathologists and staged by Dukes method. This level of staging is inadequate. The surgeons assessment of cure at the end of the operation is not an independent prognostic indicator of survival and does not add to the accuracy of prognosis when the Dukes stage is known. This data has shown that the important prognostic factors for any individual surgeon performing an operation are; Dukes stage,

the presence of metastases on IOUSS, a preoperative serum CEA of ≥ 160 u/l and the age of the patient. For the group as a whole the grade of surgeon performing the operation is also significant.

Chapter X

Conclusions

X.A. Introduction

The conclusions drawn from this thesis will be considered in four parts:

1. The use of IOE scanning for the detection of hepatic metastases at the time of primary resection of colorectal cancer.

2. The use of IOUSS for the detection of hepatic metastases at the time of primary resection of colorectal cancer.

3. The role of serum CEA estimation in patients with colorectal cancer.

4. The accurate staging of patients with colorectal cancer at the time of surgery and their subsequent follow up.

X.A.1. IOE scanning

IOE scanning is an accurate, safe, and above all, clinically applicable technique for the enhancement of CT scans to improve the detection of hepatic metastases. Anxiety because of toxic side effects published by Reinig and Sugarbaker (Reinig JW, 1987) and lack of commercial production has meant that IOE scanning has remained a research tool.

CT portography (CTAP) has become a popular technique for the investigation of hepatic metastases. It is both accurate (90%) and sensitive (91%) (Soyer P, 1992; Lindberg CG, 1993). The techniques of arteriography are well developed and the contrast agents have a documented safety record. As yet there have been no reports of adverse reactions or morbidity associated with CTAP scanning. This technique has become the pre-operative investigation of choice for imaging hepatic malignancy prior to resectional surgery. There have been reports of false positive investigations with CTAP, with up to 42% of round defects being perfusion or flow anomalies, and a false positive rate of

up to 23% in the detection of segments involved by tumour (Paterson MS, 1992; Llauger J, 1992; Lindberg CG, 1993). CTAP compares favourably with MRI and IOUSS (Soyer P, 1992, 1993) in terms of both sensitivity and accuracy, but has a higher false positive rate than either. IOE scanning in this study has a similar accuracy to that of CTAP and a very much lower false positive rate of only 15 out of 195 investigations (7,7%). The lower limit of resolution of CTAP is also similar to IOE scanning at around 1 cm (Mclaughlin RF, 1993)

The comparison of IOE scanning to DBCT in this study shows IOE scanning to give superior results in terms of the number of hepatic segments shown to be involved by tumour and in the determination of resectability of hepatic tumour.

IOE scanning fails to detect very small intra-hepatic tumour deposits. For patients undergoing resection of primary colorectal cancer, the false negative rate in the detection of small hepatic metastases was low (4.5%). In these patients, IOE scanning was used only to detect tumour within the liver, and not to determined resectability. IOE scanning cannot detect the presence of small peritoneal metastases as it has no advantage over palpation and visualisation in this regard.

IOE scanning is a repeatable investigation: there has been no evidence of either sensitisation or tachyphalaxsis to the contrast agent. However, patients are unwilling to have repeated IOE scans during their follow-up. This limited the recruitment to the study and would limit the use of IOE scanning in a clinical context.

X.A.1.a. IOUSS

Intraoperative ultrasonography is the gold standard for the premortem detection of intra-hepatic malignancy. This investigation has an accuracy of more than 90% in the detection of intrahepatic malignancy in two groups of patients studied in this thesis. The investigation has a negligible false positive rate and is more accurate than attempted biopsy in the correct identification of malignant lesions. Others have obtained similar results for IOUSS (Stewart PJ, 1993: Machi J, 1991), recently Soyer has found CTAP and IOUSS to have similar sensitivity in the detection of small metastases but IOUSS was more specific (Soyer P, 1992). IOUSS can be used at the time

of surgery for patients with colorectal cancer to improve the detection of hepatic metastases in these patients. The information gained by IOUSS is of independent significance in the determination of survival following cureative resection of colorectal cancer.

There are no practical limitations to the use of IOUSS, the equipment is inexpensive, the technique is simple and may be learned over a short period of time by general surgeons. IOUSS is the method of choice for the detection of hepatic metastases at the time of resection for colorectal cancer. Laparoscopic ultrasonography offers the same accuracy of hepatic staging during laparoscopic surgery as may be attained at laparotomy.

X.A.1.b. Hepatic resection

Two patients in this series were suitable for, and underwent hepatic resection for colorectal metastases detected at the time of their primary surgery by IOUSS and IOE scanning. Unfortunately both of these patients died of recurrent disease within 2 years of their hepatic resection. Early detection of hepatic metastases, at the time of curative resection of colorectal cancer, and their subsequent resection, has not been shown to improve patients survival in this small series.

X.A.1.c. CEA

It is becoming clear that, with the advent of IRMA test kits for serum CEA estimation, the accuracy of this investigation in the determination of prognosis and recurrence has improved.

In patients with known recurrence of colorectal cancer being staged for hepatic resection, the level of serum CEA at presentation with recurrence has a negative correlation to the resectability of the tumour. Although significant, this relationship is unfortunately of little clinical value as the spread of CEA values is so wide. A serum CEA of ≥1000 u/l at presentation with recurrence, however, gives predictive value of 92% for irresectable disease. The overall accuracy for CEA in the determination of resectability is low at 58%.

In patients presenting with colorectal cancer, elevation of serum CEA is positively correlated to the presence of hepatic metastases. In this series, preoperative CEA of 160u/l was found to have a 71% accuracy in determining the presence of metastases. Not only may the preoperative CEA give an

absolute indication of the risk of recurrence, but postoperative measurement of CEA values may also give an indication of the timing of recurrence. Elevation of CEA to > 100u/l in the postoperative period is an indicator of recurrent disease in 83% of patients.

CEA is an indicator of prognosis and timing of recurrence in 70% - 80% of the population of patients with colorectal cancer. When correctly interpreted, a rising CEA may be the only indicator of recurrence of colorectal malignancy. As such, this test represents a cost-effective and practical method indicating prognosis and of screening for recurrence.

X.A.2. Laparoscopic ultrasonography

Initially using modified endo-anal equipment and latterly custom built probes (Aloka), laparoscopic hepatic ultrasonography has been performed (Jakimowicz JJ, 1993). This small series has shown that laparoscopic ultrasonography can be performed and can provide an image quality similar to that obtained with IOUSS at laparotomy. The use of laparoscopic ultrasonography is the subject of a further investigation currently underway in the University Department of Surgery. It is likely that laparoscopic ultrasonography will become the mainstay investigation prior to laparotomy for hepatic resection and may replace all other preoperative imaging investigations. Laparoscopic ultrasonography will become a vital part of the staging laparoscopy prior to laparoscopic colonic resection for malignant disease.

X.A.3. Staging of colorectal cancer

There is no doubt that the presence of hepatic metastases from colorectal cancer is an indicator of poor prognosis. The presence of hepatic metastases is associated with a mean survival of 18 months and a negligible 5 year survival. We have used IOUSS to detect very small volume intrahepatic tumours which are at an early stage of their development. Early detection may explain the better than expected survival of patients with hepatic metastases in this series.

Survival analysis has shown that the presence of hepatic metastases detected by IOUSS at the time of operation is a prognostic indicator which is

independent of Dukes stage and preoperative serum CEA, each of which have independent prognostic value. The assessment of curative resection, including the detection of metastases by palpation, by the surgeon at operation, is not an independent indicator of prognosis. Accurate staging and follow-up of patients in this series has also revealed a significant association between junior grade of principle surgeon and poor prognosis, which also remains an independent factor after multivariate analysis.

The four factors identified in this series (Dukes stage, age, hepatic metastases and serum CEA) could be used, with appropriate weighting, to construct a perioperative staging system which, by taking into account all four independent variables, would give a more accurate estimate of prognosis than any of the variables considered singly. The number of patients in this series is too small to allow accurate weighting, a larger series will be required. However, the relevant factors have been identified and potential for improved staging recognised.

This thesis has shown that intraoperative ultrasound scanning at the time of curative resection for colorectal cancer is a practical procedure that provides independent prognostic information. This technique should be used to improve the staging of colorectal cancer at the time of operation so that both the results of surgery and adjuvant therapies can be assessed in groups of patients for whom the stage of disease has been accurately documented. Accurate matching for stage will allow the effects of different treatments on similar groups of patients to be compared. Failure to assess the presence of hepatic metastases introduces a powerful, random effect on outcome which may mask more subtle effects brought about by adjuvant treatment regimens.

It is only through improving our knowledge of malignant disease that we can hope to improve treatment and so, survival. To this end, this thesis has shown that surgeons who are treating patients with colorectal cancer, and in particular coloproctologists who may be treating large numbers of patients with malignant disease, should undertake intraoperative ultrasound scanning of the liver as a part of their operative routine.

Appendix 1 Summaries of patients with positive scans.

Introduction

These are short summaries of patients who had either a positive IOE scan and a negative IOUSS at the time of operation or a negative IOE scan and a positive IOUSS. They are included to give an indication of the reasoning in each case as to the final confirmation of the presence or absence of metastases.

The details of each patient with confirmed metastases

1. Patient number 3. 65 year old woman, curative resection of a Dukes B carcinoma of the caecum. No palpable metastases, IOUSS normal, developed metastases on the second IOE scan confirmed by the two following scans. Final CEA was 37 u/l. Status: confirmed hepatic metastases.

2. Patient number 7. 61 year old man. A low rectal carcinoma, Dukes B resected by abdomino perineal resection. Hepatic metastases detected by palpation and IOUSS at the time of operation and confirmed by follow up IOE scanning. CEA at final scan 6350 u/l. Status: confirmed hepatic metastases.

3. Patient number 12. 62 year old man. Sigmoid colectomy for a Dukes A adenocarcinoma of the descending colon. Palpation of the liver was normal. IOUSS detected a 12 mm metastases in segment V. The first three IOE scans were normal; however, the final IOE scan detected a single metastasis in segment VIII. The patients' CEA was 97 u/l prior to resection, fell to normal during his early follow up and had risen gradually to 61 at the time of re-presentation of the metastases. Status: confirmed hepatic metastases.

4. Patient number 17. 88 year old woman. Right hemicolectomy for a Dukes B carcinoma of the transverse colon. Three hepatic metastases were palpable at the time of operation and confirmed by IOUSS. The first IOE scan detected all three metastases. CEA at the time of the IOE scan was 101 u/l. Status: confirmed hepatic metastases, died.

5. Patient number 18. 78 year old man. Anterior resection for a Dukes C1 carcinoma of the rectum. This was tethered to bowel and bladder at operation but all of the tumour was resected. There were no palpable hepatic metastases. IOUSS revealed a single 14 mm metastasis in segment VI. A

metastasis was confirmed on the first IOE scan but placed in segment VIII. On the third scan the metastasis was correctly sited in segment VI and was 10 cm in diameter. CEA was 30 u/l before primary resection. The CEA at the time of the last IOE scan was 30 u/l. Status: confirmed hepatic metastasis.

6. Patient number 25. 56 year old woman. Anterior resection and hysterectomy for a locally extensive mucinous Dukes C1 carcinoma of the upper rectum. Palpation at operation revealed three metastases, one each in segment II, VI and VIII, these were 20, 10 and 20 mm in diameter respectively. On IOUSS, these were found to be cysts, the largest of which (in segment VI) contained internal septa and debris. This was defined as a cystic metastasis at the time of the scan. The presence of multiple complex cysts was confirmed on the first IOE scan. The patient died before the second scan. CEA at the time of the IOE scan was 92 u/l. Status: confirmed hepatic metastases.

7. Patient number 26. 82 year old woman. Right hemicolectomy for Dukes B adenocarcinoma of the transverse colon. The tumour was tethered to bowel and a single hepatic metastasis was detected by palpation. IOUSS detected the same 14 mm metastasis in segment II. IOE scan was reported as showing two 1 cm metastasis one in segment II and the other in segment VIII. The patient died before the second IOE scan. CEA at the time of death was <30 u/l. Status: confirmed hepatic metastases.

8. Patient number 57. 60 year old man. Right hemicolectomy for a Dukes B carcinoma of the ceacum. Palpation at operation revealed a single 10 mm metastasis in segment II. IOUSS detected a large 10 cm ill-defined mass in segment V. Biopsy of this confirmed the presence of metastatic adenocarcinoma. IOE scan confirmed the same metastasis. The patient died before the second IOE scan was performed. CEA at presentation was 84 u/l. Status: confirmed hepatic metastases.

9. Patient number 64. 78 year old woman. Sigmoid resection for a Dukes A adenocarcinoma of the recto sigmoid junction. Palpation at operation revealed a 10 cm metastasis in segment IV. This was confirmed on IOUSS and the presence of two more metastases in segments II and III was confirmed. The largest metastasis was confirmed by biopsy. IOE scanning suggested five metastases all in segment IV. The patient died before the second IOE scan. CEA at the time of the first scan was 194 u/l. Status:

confirmed hepatic metastases.

10. Patient number 82. 62 year old man. Abdomino perineal resection for a Dukes C1 carcinoma of the rectum. There were no palpable metastases, although IOUSS detected more than 10 small metastases through both lobes of the liver, two of which were confirmed on the first IOE scan. Subsequent scans revealed one of the metastasis to be of increasing size. The final IOE scan failed to detect any metastases and is a false negative. Status: confirmed hepatic metastases.

11. Patient number 89. 70 year old woman. Right hemicolectomy for Dukes C2 carcinoma of the colon. There were no palpable metastases. IOUSS detected 4 metastases in segments III, IV and V. A single metastasis, 8 mm in segment VII, was also detected by the first IOE scan. CEA at the time of the IOE scan was 500u/l. The patient died before the second scan. Status: confirmed hepatic metastases.

12. Patient number 90. 61 year old man. Anterior resection for a Dukes C1 adenocarcinoma of the rectum. Palpation revealed two metastases confirmed by IOUSS, in segments VI and VIII, 35 and 40 mm in diameter. These were identified by IOE scanning as being in segments VI and VII. This patient underwent hepatic resection and the two lesions were confirmed. The IOE scans of the remaining liver in the follow up period were normal. Status: confirmed hepatic metastases.

13. Patient number 99. 77 year old man. Abdomino perineal resection for a Dukes C1 mucinous carcinoma of the rectum. IOUSS and palpation of the liver at the time of operation were normal, as were the first and second IOE scans. The third scan revealed three metastases, each 2 cm in diameter, in segments IV, VI and VII. The fourth scan revealed 7 metastases of various sizes scattered throughout the liver. CEA at the time of the last scan was >1000 u/l. Status: confirmed hepatic metastases.

14. Patient number 106. 62 year old man. Reversal of a Hartmanns operation for carcinoma of the transverse colon. The original tumour was Dukes C1. Palpation of the liver at reversal was normal, as was IOUSS. The first IOE scan was also normal, the second detected a 30 mm metastasis in segment V. CEA at the time of the second IOE scan was 182 u/l. Status: confirmed hepatic metastases.

15. Patient number 108. 43 year old man. Sigmoid resection for a Dukes C1 carcinoma of the colon. Palpation of the liver failed to detect any metastases. IOUSS detected a single 20 mm mass in segment VII. This was also apparent on the first IOE scan. The patient underwent a course of chemotherapy and resection of the right lobe of the liver. On pathological sectioning, the lesion had decreased in size. There was no evidence of carcinoma, only an area of fibronodular hyperplasia. The patient was re-admitted with local and hepatic recurrence in Feb. 1994 and died. Status: confirmed hepatic metastases.

16. Patient number 111. 68 year old woman. Subtotal colectomy for a Dukes C1 carcinoma of the rectum. Palpation at the time of operation detected a 15 mm metastasis in segment VI. This was confirmed by IOUSS, as was the presence of several cysts. The first IOE scan failed to detect any lesions. The second IOE scan detected 4 metastases. CEA at the time of the second IOE scan was 101 u/l. Status: confirmed hepatic metastases.

17. Patient number 113. 76 year old male, curative resection of a Dukes C2 carcinoma of the transverse colon. No palpable metastases, single 10 mm metastases in segment VI on IOUSS confirmed on the second and fourth IOE scan, with 2 metastases on the second IOE scan, in segments VI and VIII and only one metastases on the final scan in segment VIII. Follow up CEA at 24 months was 1630 u/l. Status: confirmed hepatic metastases.

18. Patient number 141. 58 year old man. Right hemicolectomy for a Dukes B adenocarcinoma of the ceacum. Palpation at operation revealed the presence of a single 12 mm metastasis in a subcapsular position in segment V. This was confirmed on IOUSS which showed the liver to be largely replaced by metastases. Three IOE scans failed to detect any lesion. CEA at the time of the last IOE scan was < 30 u/l. The patient, who failed to attend for his fourth IOE scan, was admitted more than three years after the original resection with hepatic metastases and local recurrent disease. Although there was no biopsy taken at the time of operation, there was no doubt that the liver was full of metastases. There was no evidence of cirrhosis or cysts. Status: confirmed hepatic metastases.

19. Patient number 154. 43 year old man. Anterior resection for a Dukes B adenocarcinoma of the upper rectum. Palpation of the liver at operation was normal. IOUSS revealed a 15 mm metastasis in segment IV. The first

IOE scan detected a metastasis in segment IV and also a metastasis in segment V. CEA at the time of scanning was 74 u/l. The patient died before the second IOE scan. Status: confirmed hepatic metastasis.

Patients who have had a positive IOE scan in whom metastases have not been confirmed.

1. Patient number 4. 57 year old woman. Sigmoid resection for a Dukes C2 adenocarcinoma of the colon. A single small nodule on the liver was biopsied after detection by palpation alone. No metastases on IOUSS. The biopsy was negative, The first, third and fourth IOE scans were negative, the second was a false positive. CEA at the time of the second IOE scan was 31. CEA at the time of the last scan was 204 u/l, indicating the possibility of local recurrence. Status: no hepatic metastases. This represents a false positive IOE scan.

2. Patient number 11. 79 year old woman. Right hemicolectomy for a Dukes B carcinoma of the caecum. Palpation of the liver at the time of operation was normal, as was IOUSS. The first, second and fourth IOE scans were normal, the third suggested a 10 mm metastasis in segment VI. CEA at the time of presentation was 545 u/l and remained below 50 for the duration of the follow up. Status: confirmed no hepatic metastases.

3. Patient number 14. A 77 year old woman with a pre-operative CEA of 30 u/l, at operation was found to have a mobile cancer of the upper rectum above the peritoneal reflection. Curative resection was undertaken with a restorative stapled anastomosis. There was no evidence of metastases at operation either by palpation or by intraoperative ultrasonography. Pathological examination revealed a 2 cm protuberant adenocarcinoma, 6 cm from the distal resection margin of the rectum (Dukes B). The first post operative IOE scan suggested the presence of a single small metastasis in segment V. This did not appear on subsequent IOE scans over the 18 month period of follow up. Status: no hepatic metastases. This represents a false positive IOE scan.

4. Patient number 15. 76 year old man. Abdominoperineal resection for a Dukes B adenocarcinoma of the rectum. Palpation of the liver at operation,

IOUSS and the first IOE scan were all normal. The second IOE scan suggested three metastases in segments II, III and V. This was supported by a rise in CEA to 100 u/l. However, the third and fourth IOE scans did not show any evidence of metastases and the CEA fell to 67 u/l over a period of 12 months. Preoperative CEA was 93 u/l. Status: confirmed no hepatic metastases. The patient died 1186 days after his operation. There was no evidence of hepatic metastases at the time of death.

5. Patient number 16. An 80 year old woman with a pre-operative CEA of 66u/l. At operation she was found to have a mobile carcinoma of the caecum. Curative resection was undertaken with a restorative single-layer anastomosis with absorbable suture material. There was no evidence of metastases at operation either by palpation or by intraoperative ultrasonography. Pathological examination revealed a 2.5 cm protuberant tumour of the caecum, 17 cm from the proximal resection margin (Dukes B). The first preoperative IOE scan suggested three metastases in segments V, VI and VIII of the liver, and measuring 8 mm, 8 mm and 6 mm in diameter respectively. Preoperative ultrasonography had not detected any abnormality and subsequent IOE scans over the period of the study failed to detect any abnormality. This represents a false positive IOE scan. Status: no hepatic metastaes.

6. Patient number 24. 46 year old woman. Sigmoid resection for a Dukes C1 carcinoma of the colon. There were no palpable metastases, IOUSS was clear as were the first three IOE scans. The final IOE scan suggested a single small metastasis in segment VII. CEA at the time of the last scan was 30 u/l. CEA at the time of primary resection was also 30 u/l. The presence of metastases in this patient was not confirmed. Status: no hepatic metastases.

7. Patient number 31. 80 year old woman. Right hemicolectomy for a Dukes B carcinoma of the ceacum. Palpation of the liver at operation was normal as was IOUSS. The first, third and fourth IOE scans were normal, the second showed a 22 mm metastasis in segment II. The CEA prior to operation was 30 u/l and remained at that level through out her follow up. Status: no hepatic metastases.

8. Patient number 33. 70 year old man. Total colectomy for a stenosing carcinoma of the caecum. Palpation at operation revealed two lesions on the surface of segment V and VIII. These were shown to be cysts on IOUSS;

there were no other lesions. The first, third and fourth IOE scans were normal, the second scan showed a 5 mm lesion in segment 8 in a subcapsular position. CEA at the time of the last IOE scan was 30 u/l. Status: confirmed no hepatic metastases.

9. Patient number 35. 76 year old man. Anterior resection for a Dukes C1 adenocarcinoma of the rectum. Palpation and IOUSS at the time of operation were normal as were the first and third IOE scans. The second scan suggested a metastasis in segment II. CEA at operation was 131u/l. Three months after surgery it was 135 u/l then 76 u/l, 30 u/l, 93 u/l, 73 u/l . The patient failed to attend for his final scan because of recurrence of local disease. Status: no hepatic metastases.

10. Patient number 36. An 80 year old man with a pre-operative CEA of 30u/l, who had an emergency subtotal colectomy for an obstructing carcinoma of the sigmoid colon. The primary tumour was mobile and a restorative single layer anastomosis was made with interrupted absorbable sutures. Palpation of the liver by the surgeon revealed apparent metastases in segments, II, IV, V and VI. These were 22 mm, 10 mm, 10 mm and 10 mm in diameter respectively. Intra-operative ultrasonography revealed three cysts in segments IV, V and VI. The lesion in segment II was not seen. A single IOE scan in the post-operative period suggested metastases in segments VI, V, and VIII, each 10 mm in diameter. Pathological examination of the specimen showed a 3.3 cm stenosing Dukes C1 carcinoma 5 cm from the distal resection margin. There were also 9 adenomas in the resected specimen. Preoperative hepatic ultrasonography failed to detect any abnormality . This patient did not enter the IOE follow up phase of the study and when last seen at a clinic 6 months after surgery was well with a CEA of 55u/l. This represents a false positive IOE scan. Status: no hepatic metastases.

11. Patient number 72. 66 year old woman. Right hemicolectomy for a Dukes C1 carcinoma of the caecum. Palpation of the liver at the time of operation was normal as was IOUSS. The first, second and third IOE scans were also normal. The final IOE scan suggested three metastases of 20 mm each, in segments IV, VI and VIII. CEA prior to surgery was 44 u/l and at the time of the last scan was 30 u/l. Although the lesions seen on the last IOE scan may have been metastases this was not confirmed by any other

investigation. The patient died 677 days after surgery. Unfortunately the presence of hepatic metastases was not confirmed at the time of death. Status: possible hepatic metastases not confirmed

12. Patient number 80. 69 year old man. Anterior resection for a Dukes C1 adenocarcinoma of the colon. Two small lesions were detected at operation by palpation on the surface of segments V and VI. These were not detected by IOUSS which identified subcapsular cysts in the same position. They were detected by the second IOE scan and reported as metastases in a subcapsular position in segments VI and VIII, each now 2 cm in diameter. CEA at the time of the final IOE scan was 60 u/l. The patient became symptomatic and no further scans were performed. These lesions were not confirmed as metastases within the criteria of the study and so this represents a false positive IOE scan. Status: no hepatic metastases.

13. Patient number 85. A 69 year old man with a pre-operative CEA of 65 u/l, at operation had potentially curative anterior resection of a Dukes C1 carcinoma at the peritoneal reflection of the rectum. The tumour was locally invasive being fixed to the left pelvic side wall, the dome of the bladder and the left ureter. There was no evidence of trans-celomic spread or of hepatic metastases either on palpation or intra-operative ultrasonography. The first post-operative IOE scan revealed two apparent metastases in segments IV and VII each of 8 mm diameter. Three subsequent scans over the 18 month period of the study failed to confirm the presence of any abnormality in the liver. This represents a false positive IOE scan. Status: no hepatic metastases.

14. Patient number 137. 46 year old man. Anterior resection and resection of bladder for a Dukes C2 carcinoma of the rectum. Palpation of the liver at the time of the operation was normal as was IOUSS. The first and second IOE scans were also normal. CEA prior to surgery was 30 u/l. The third IOE scan suggested a 7 mm metastasis in segment VII. This patient had a local recurrence of his disease and a fourth scan was not performed. Status: possible hepatic metastases not confirmed.

15. Patient number 139. 44 year old man, curative resection of a Dukes B carcinoma of the right colon, preoperative CEA was 54 u/l. There were no palpable metastasis, no metastases on IOUSS. The second IOE scan showed a single 10 mm metastasis in segment III. The CEA was 58 u/l (within the

normal range). He became clinically unwell and had no further imaging. This represents a false positive IOE scan. Status: no hepatic metastses.

Appendix 2

Computerised storeage of data.

A.2.A. Introduction

It was obvious from the inception of this project that there would be a large amount of data collected. The most efficient way to store the data in a manageable form was in a computerised database. The database and the software to run the database was developed within dBase III plus, a commercially available database package (Ashton Tate Corp.). There were a number of advantages to this system and some disadvantages. All of the database design, construction and programming was done by the author, WFAM. The aim was to produce databases which would contain all of the information from each patient in such a way that the various parameters could be compared and the patients could be sorted on the basis of any parameter. All of the patients' details were stored and, although a duplicate paper copy was kept, this was only as a safe guard against data loss. The programming feature of dBase III plus allowed the author to produce a customised package which, when installed, would allow the collection and indexing of patient data by any operator without previous knowledge of dBase III plus.

A.2.B. Equipment

All of the database construction and programming was performed using dBase III plus and "dBase III plus" Administrator. The computer used was an IBM PS/2 286 AT. Information concerning the use of "dBase III plus" and programming was obtained from "dBase III plus made easy", Miriam Liskin, Osborne, McGraw-Hill, Berkley, California and from "dBase III plus, Programmers Reference Guide" Edward Jones, Howard W. Sams & Company, 4300 West 62nd St, Indianapolis, Indiana. Both of these texts were considerably more useful than the manuals supplied with the program.

A.2.C. Design

The database was designed on paper in the first instance. A list of the data to be collected was made and used to construct a data collection sheet. The data files for each patient were constructed by converting the outline structure of the sheet into screens in the computer program. Each screen matched one of the data collection sheets, not only in appearance but in the type of information in each field.

Each file in the database can contain a maximum of 127 fields. As the data entry sheets contained many times that number of fields (580 in total) it was necessary to construct a number of files for each patient, each file being a separate database in its own right. These separate databases each contained identical key fields which allowed the separate databases to be linked (related) together for data input and analysis.

There were eight separate files, each containing information on a different aspect of the patients' history, examination or investigation. Each file contained four identical key fields, these were for the patients' first name, last name and their date of birth. These three strings; "LASTNAME", "FIRSTNAME" and "DOB" were joined in a fourth field called "LINK" . Every patient file in each of the databases used in this thesis contain this "LINK" field. Because of the highly individual nature of these three fields, the identifier "LINK" could be considered as unique for each patient.

A.2.D. Data files.

There are 8 data files of various length and complexity for each patient. Each of these is linked to a screen construction file. The construction of these screens is such that they are identical to the paper 'Patient Data' sheets and so transfer of data is as straight forward as possible. The screens contain information regarding how information should be put into the computer, its format, and where required codes that are used to identify various stages of disease or clinical findings. The screens are designed to ensure that data is put into the computer in a consistent manner. Failures of consistency have made data analysis more difficult.

Within "dBase III plus", data can exist in a number different formats. The data is stored in a field and each field must have a format. Data can only be

entered if it conforms to the format of the field. If an attempt is made to enter data which does not conform it will be rejected. The formats are: character, date, numeric, logical and memo.

A.2.E. Basic design

The database is designed so that patient data could be put in by anyone with basic computer skills and no special knowledge of "dBase III plus". Apart from the commands required to gain access to the database and the codes to access the protected files all of the basic functions of the program are menu driven.

A.2.E.1. Protection

To gain access to the database the operator must use a code word followed by their name and an individual code number. This gives three levels of protection to the program and the data within it. All of the database information is encrypted so that the data files can not be read without first going through the codes at the beginning of the program.

A.2.E.2. Data entry

Once access has been gained to the program the operator is given a menu of the facilities within the program (*Fig 1*).

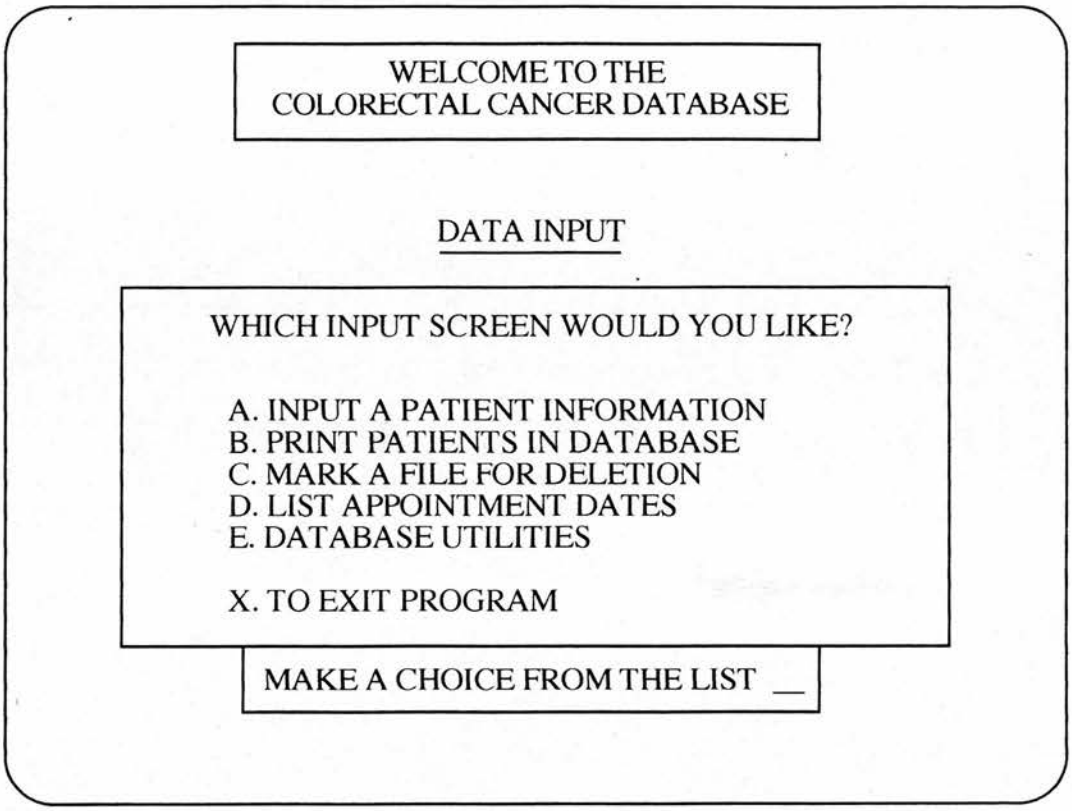

Fig 1 opening menu from the colorectal cancer database.

Choice " A " initiates access to the patients' files menu. In order to gain access to the files, it is necessary to input the patients' first name, last name and date of birth. The program will then search the database for a match. If none existed it will then search for an inexact match on the last name alone. If there is no match for the last name, the program will display all the patients with a last name whose opening string of letters matches those of the input data. For instance if the operator inputs "Charles Smith" and date of birth "22/01/27", this will match patient 106 exactly and this patients' records will be accessed. Just typing "Smith" will bring up the two patients in the database with the last name Smith. If only the letter S is supplied a list of the 17 patients with a last name beginning with 'S' will appear. The operator will then be asked to choose one of the records to view, or to create a new set of files based on the information used for the patient search, in this case the letter 'S'. Every time a patient is put into the database the same procedure is used, this prevents patients having two or more sets of files produced. If it is indeed a new patient, the search information (last name, firstname, and data of birth) would

then be used to initiate and add to the index a blank set of files for that patient. These files could then be opened and filled (*Fig 2*).

During the two years of data input, this system only failed twice. Once the computer hard disc cross linked one of the "dBase III plus" files to a file in "Reference manager", another database program on the hard disc and this had to be corrected manually. On the second occasion, unauthorised access to the computer resulted in reallocation of one of the keys on the keyboard. This allowed a non-alphanumeric character to be typed into an index field corrupting the index. This was corrected by rebuilding the database from backup. The software has never failed and there was no duplication of notes and no inadvertent addition of the wrong information into the wrong patients' files.

Each patient's file can be accessed as often as required to add and edit data as they became available.

The follow up files are accessed from the second level menu and are indexed in a similar manner. Patients can only have follow up files if they already exist in the patient identification database. Once accessed, the follow up menu will allow a choice of all of that patient's follow up files in chronological order. If no file existed, a new one could be generated and then filled. Again the system will search for all similar patients prior to the initiation of a new set of files. When completed, the files are automatically saved as they were closed.

A.2.F. Storage

All of the data was stored on the hard disc of the computer and on floppy discs. The floppy disc information was encrypted, the discs were divided into sets. one set for daily backup, one for weekly and one (stored at a different location) for a monthly backup. As mentioned the backups were required on two occasions to reconstruct the database when it failed.

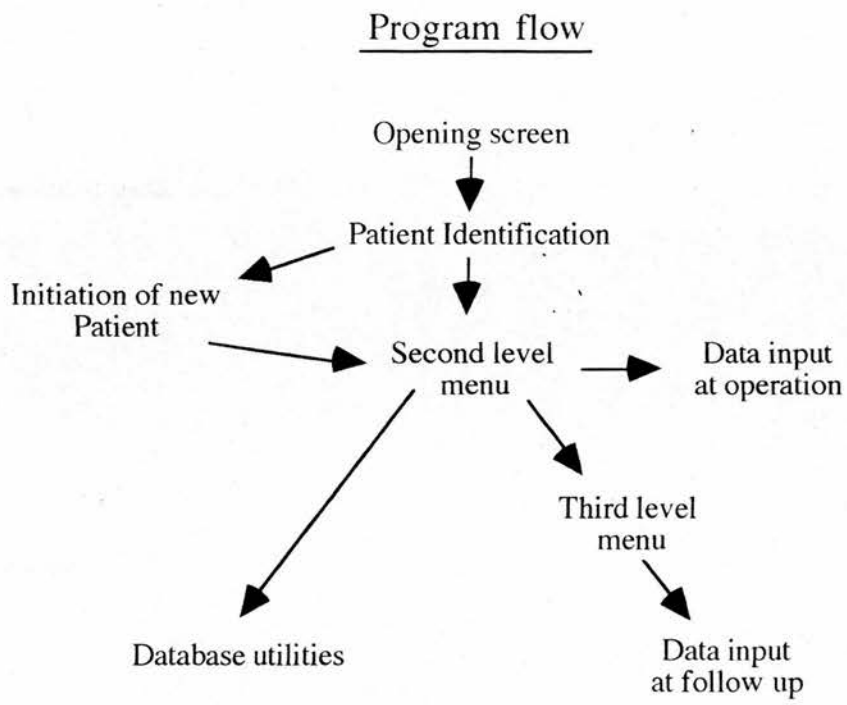

Fig 2 Program flow for the input of information into the colorectal cancer database.

A.2.G. Analysis

Once all of the data had been collected and prior to analysis, it was necessary to check the database for "rubbish". There were a number of fields which were completed in an inconsistent manner, either because the questions were ambiguous or because the nature of the data was not exact. The major problems occurred with fields which required a Yes / No answer but were not logical fields. These were then filled in as ether Y for Yes or T for True, and N or F for the negative response. Unfortunately, "dBase III plus" can only search for exact matches of characters or for characters within a string of characters. The use of either Y or T for a response meant that either inexact search parameters had to be used or all of the fields containing this type of data had to be corrected to contain either T,F or Y,N responses. The latter approach was chosen and all of the fields of this type were "cleaned" to contain only one type of response. A number of short programs were written for this purpose.

Once all of the data had been cleaned and checked, analysis was performed. As the central question was the comparison of the results of one investigation

against another, most of the analysis was comparative. In order to compare two databases it is necessary to link them so the same patients in each database can be compared. "dBase III plus" allows databases to be "related", provided they contain a field which is the same in each database and on which the database is indexed. The "link" field was used for this. As all of the patients were entered into each of the databases in the same order, it was also possible to use the unique number allocated to each patient by "dBase III plus" called RECNO(). This is a chronological record of the order in which files are entered into the database. As all the files for one patient were created at the same time, it was a second unique identifier for each patient. RECNO() could not be used for the follow-up files as they were not all created at the same time and so had different record numbers for records belonging to one patient.

Once two or more databases had been related, then a search for patients fulfilling any number of criteria from any number of the databases could be constructed. For instance, by relating the blood result database COLONCAB to the intraoperative ultrasound result database COLONCAI, it was possible to list the CEA result for each patient with hepatic metastases at operation. This type of search can be carried out with any combination of scope of patients or criteria for the search.

A.2.H. Discussion

With hindsight, there are a number of features of this database which were unnecessary. The eight separate databases containing a total of 548 fields was more comprehensive than was required. A number of the fields related to data which was not collected or not available from the majority of the patients. These fields were discussed at the design stage and included because of the general feeling thst it was better to include too much rather than let data go unrecorded. This was an error: these largely empty fields have cluttered up the databases and slowed down data entry and recovery. The ideal database should contain fields for available and important information. The maintenance of a database in clinical projects is difficult and is made more so by having larger numbers of fields to fill. Failure to complete each patient's record leads to a dilution of the number of patients that can be used for analysis. In order to complete all of the data, a full time research nurse, JC, was employed to record the details of the IOE scans and to search for the data that was missing. In all cases all of the data that was available for each patient was recorded

prospectivly. For most patients there were a number of fields left blank for investigations which were not performed.

Further development of this data base would have allowed all of the patients to be called for their investigations directly from the database and all of the clinic appointments and letters to have been arranged from the computer. This was not done for a number of reasons but principally because the programming of the database was ongoing and by the time a clinic appointment program had been written and checked most of the patients had already been documented in a follow up diary and their scans arranged. The number of patients entered into the database was much lower than had been envisaged. The diary system worked perfectly for the numbers involved and was both simple and reliable. If larger numbers of patients had been involved then computerisation may have held some advantages, particularly in booking and sending for the patients to come in for follow up scans.

The "dBase III plus" software was robust and reliable. The program itself did not cause any problems and worked faultlessly throughout. Programming in "dBase III plus" was also straight forward and allowed the development of a set of databases to collect a large amount of data on a moderate number of patients. It is undoubtedly a powerful tool which can allow inexperienced programmers to produce useful software with the minimum of difficulty.

Computerisation of data should not be seen as the answer to all problems in data collection and storage. In particular, the ability to store large amounts of data should not be used as an excuse to collect more data. Data should only be collected if it is of relevance to the question being asked and if it will provide or help to provide an answer. Unfortunately this was not the case with all of the data collected in this database. More critical planning of the content could have led to a much slimmer database with fewer empty spaces. The only advantage to collecting large amounts of data is that some unexpected relationship may turn up during the analysis. However, the likelihood of completely unexpected relationships being discovered are remote. The only data which has proved to be of worth was that which was collected with the express intent of providing an answer to a specific question.

A.2.I. Programs

A number of the key programs for the colon cancer database have been included

in appendix 3. All of the programs were written by the author without the assistance of any other programmer. In total 116 programs were written for the LIVERCA database and the COLONCA database. This does not include the construction of the actual databases and the screens for data input. A small number of programs have been written not directly related to the management of the databases. These perform basic statistical analysis of the data. One such program calculates Chi Squared while another calculates sensitivity, specificity, and accuracy.

Further development of the COLONCA database had not been undertaken. However, it will be possible to use this program as the basis for a computerised colorectal clinic with regulated follow up of all patients and automatic recall to the out-patient clinic and for colonoscopy. By using the database to run a clinic, all of the data from patients' follow up would be collected prospectivly and subsequent analysis would be both rapid and straight forward.

There is no doubt that in the future, patients' clinical details will be collected onto databases as part of the daily routine of admission. The course of the patients' admission will be prospectivly recorded as will the results of their investigations and their outcome. This will result in large databases from which data can be drawn and analysed. It will be possible to insert key fields to record particular information in response to relevant questions. In this way, large patient databases will speed up data collection for research projects such as this. Both the LIVERCA database and the COLONCA database are prototypes for this type of data collection.

Appendix 3

Computer programmes

And Databases

Introduction

These are a sample of the 117 programs that have been written to allow the data collected on patients within this study to be correlated. The file structures for two of the databases used for the COLONCA database are also listed, as is a summary of the contents of the Survival.dbf file.

Programme titles

COLOPEN3

This is the first of the opening programs. It checks that all of the databases are available and that their indexes are also present.

COLOPEN2

This is the second of the opening programs. It welcomes the user to the database and displays the various options from this programme. To add patients to the database or to add information to a patient who already exists, the user must choose "A" from the menu.

OPEN

This is the last of the opening screens. It requires the user to input patient details in order to select the appropriate patient from the database or to initiate a new set of screens for a new patient if required.

NOTECHEK

The data gained by OPEN is used in NOTECHEK to check all of the patients in the database for a match. If no match exists, then all of the patients with the same last name will be presented. If there is no match for the last name in full, then any patients with a last name which has an identical string of letters

beginning with the first letter of the last name will be presented.

COLINIT

If no match is found by NOTECHEK, then the user is asked if a new set of files should be created for the data which had been used for the search.

These are just a sample of the programmes that have been written during this thesis. In total 117 programmes have been written, all of them by WFAM. There has been no external programming advice.

```
* PROGRAM.: COLOPEN3.PRG
* Author..: Tony Miles
* Begun on October I, 1990
* Notice..: Copyright to University Of Edinburgh
* Notes...: Opens the files and the indexes for colon study
*           Master Program
CLEAR
*            FIRST BUILD THE ENVIROMENT TO FOR THE SCREEN

CLEAR ALL
SET STATUS OFF
SET BELL OFF
SET HEADING OFF
SET HELP OFF
SET MENU OFF
SET SAFETY OFF
SET SCOREBOARD OFF
SET TALK OFF
SET DELETED ON
SET DATE BRITISH
STORE SPACE(1) TO m_ans
STORE SPACE(1) TO m_answ
STORE SPACE(1) TO m_ansn
*             SET UP ALL OF THE INDEX FILES TO USE IN THE PROGRAM

USE COLONCA.DBF INDEX CA.NDX
USE COLONCAP.DBF INDEX CAP.NDX
USE COLONCAO.DBF INDEX CAO.NDX
USE COLONCAU.DBF INDEX CAU.NDX
USE COLONCAI.DBF INDEX CAI.NDX
USE COLONCAR.DBF INDEX CAR.NDX
USE COLONCAB.DBF INDEX CAB.NDX
USE COLONCAC.DBF INDEX CAC.NDX
CLOSE DATABASES
DO COLOPEN2.PRG

*                     RETURN THE SCREENS TO THE DEFAULT
CLEAR ALL
SET ESCAPE ON
SET STATUS ON
SET BELL ON
SET HEADING ON
SET HELP ON
SET MENU ON
SET SAFETY ON
SET SCOREBOARD ON
SET TALK ON
CLEAR
```

```
* Program..: COLOPEN2.PRG
* Author...: Tony Miles
* Date.....: October 23, 1990
* Notice...: Copyright University of Edinburgh
* Notes....: Opens the screens for Colon Cancer Database
*            called from COLOPEN.PRG
DO WHILE .T.
*           Writes the opening screen
m_ans = ' '
   @ 2,32 SAY "WELCOME TO THE"
   @ 3,26 SAY "COLORECTAL CANCER DATABASE"
   @ 1,23 TO 4,54 DOUBLE
   @ 6,34 SAY "DATA INPUT"
   @ 7,34 TO 7,43
   @ 9,22 SAY "WHICH INPUT SCREEN WOULD YOU LIKE?"
   @ 12,23 SAY "A. INPUT A PATIENT INFORMATION"
   @ 13,23 SAY "B. PRINT PATIENTS IN DATABASE"
   @ 14,23 SAY "C. MARK A FILE FOR DELETION"
   @ 15,23 SAY "D. LIST APPOINTMENT DATES"
   @ 16,23 SAY "E. DATABASE UTILITIES"
   @ 18,23 SAY "X. TO EXIT PROGRAM"
   @ 11,16 TO 19,61 DOUBLE

*                 THIS IS THE END OF SCREEN CONSTRUCTION

   choice = space(1)   && Initiates the memory variable

   @ 20,24 SAY "MAKE A CHOICE FROM THE LIST" GET choice PICTURE '!'
   @ 19,22 TO 21,54
   READ

*                to find out if answer is in range of reply
      DO WHILE .NOT. choice $ "ABCDEX"
        choice = " "
        @ 22,0
      @ 22,10 SAY "YOU MUST CHOOSE FROM THE LIST ABOVE" GET choice PICT
        READ
       ENDDO

*       Print choice and ask for verification
   @ 22,0
   @ 20,24 SAY "YOUR CHOICE IS                " + choice
   @ 23,0
   answer = " "
   @ 22,23 SAY " ENTER. OR N. TO RE-ENTER    " GET answer PICTURE "!"
   @ 21,22 TO 23,54
   READ


                IF answer = "N"
                LOOP
                ENDIF

 answer = ' '
* NOW GOES ON TO THE DO CASE BELOW

* TO  FIND OUT WHICH SUB PROGRAM TO DO

   DO CASE
     CASE choice = "A"
        DO OPEN.PRG
```

```
         IF m_ans = 'X'
            CLEAR
            LOOP
         ENDIF
         DO COLON.PRG

      CASE choice = "B"
         DO COLLIST.PRG
      CASE choice = "C"
         DO ERASE.PRG
      CASE choice = "D"
         DO LISTFILE.PRG
      CASE choice = "E"
         DO UTILITY.PRG
      CASE choice = "X"
         RETURN TO MASTER
      OTHERWISE
         DO WARNING.PRG
   ENDCASE


CLEAR
ENDDO
```

```
* Program..: OPEN.PRG
* Author...: Tony Miles
* Date.....: DEC 6, 1990
* Notice...: Copyright to the University of Edinburgh
* Notes....: Program for the identifiiication of
*            patients
*            called from COLOPEN2.PRG


*     THIS IS THE KEY FILE IN THE DATABASE IT OPENS THE
*     FIELDS ON EACH NEW PATIENT AND WILL STOP DATA GETTING MIXED UP
*     IT WILL ALSO ALLOW PATIENT INFORMATION TO BE PUT IN FROM ANY SCRI

m_opengo= .T.

DO WHILE m_opengo
m_goback = .F.
m_initgo = .F.
   CLEAR
   @ 5,28 SAY "PATIENT IDENTIFICATION"
   @ 4,25 TO 6,53 DOUBLE
   @ 8,17 SAY "ACCURATE PATIENT IDENTIFICATION IS VITAL TO THE"
   @ 9,17 SAY "RUNNING OF THIS PROGRAM"
   @ 10,17 SAY "IF THE INFORMATION IS INACCURATE YOU WILL "
   @ 11,17 SAY "LOSE YOUR DATA FOREVER"
   @ 7,15 TO 12,65 DOUBLE
   @ 14,20 SAY "LASTNAME"
   @ 16,18 SAY "FIRST NAME"
   @ 18,15 SAY "DATE OF BIRTH"
   @ 13,13 TO 19,67 DOUBLE

   m_ans = ' '
   @ 20,30 SAY "TO GO ON PRESS ANY KEY ,"
   @ 21,20 SAY "TO GET TO THE OPENING MENU PRESS X" ;
     GET m_ans PICTURE '!'
   @ 19,18 TO 22,62
     READ
      IF m_ans = 'X'
         RETURN
      ENDIF
   m_ans = ' '
*  The next section initiates the public momory variables
*  for the identification of the patients

   PUBLIC m_last, m_first, m_dob, m_ednum, m_link, m_date
   m_ednum = 0
   m_last = SPACE(25)
   @ 14,30 GET m_last PICTURE "!!!!!!!!!!!!!!!!!!!!!!!!!"
   READ
   STORE LTRIM(TRIM(m_last)) TO m_last
   m_first = SPACE (25)
   @ 16,30 GET m_first PICTURE "!!!!!!!!!!!!!!!!!!!!!!!!!"
   READ
   STORE LTRIM(TRIM(m_first)) TO m_first
   m_dob = CTOD ('  /  /  ')
   @ 18,30  GET m_dob
   READ
   m_link = SPACE(40)
   STORE m_last+m_first+STR(YEAR(m_dob),4)+STR(MONTH(m_dob),2);
   +STR(DAY(m_dob),2) TO m_link
```

```
@ 20,0 CLEAR
   m_ans = " "
   @ 20,20 SAY "IF CORRECT PRESS ENTER. "
   @ 21,20 SAY "PRESS N TO RE-ENTER X TO EXIT" GET m_ans PICTURE "!"
   @ 19,18 TO 22,62
   READ
      DO CASE
         CASE m_ans = "N"
         LOOP
         CASE m_ans = "X"
         CLEAR
          RETURN
         OTHERWISE
         DO NOTECHEK.PRG
      ENDCASE
      CLEAR
      IF m_goback   && THIS SENDS YOU BACK TO PTID SCREEN
         LOOP
      ENDIF
* This ends the identification of the patients and the check to
* make sure that they are not already in the database

* The next section initiates a new set of screens for patients
* not already in the database
   IF m_initgo
      m_ans = ' '
      DO COLINIT.PRG   &&  INITIATES THE NEW SCREENS
   ENDIF
   IF m_goback
   LOOP
   ENDIF
m_opengo = .F.
ENDDO
RETURN
```

```
* Program..: NOTECHEK.PRG
* Author...: Tony Miles
* Date ....: October 23, 1990
* Notice ..: Copyright University Of Edinburgh
* Notes....: Checks to see if a patient is already in the
*           database
* Open the data base, index, and screen to use
m_ans = ' '
CLEAR
DO WHILE .T.
* FInd out if there is a match in the file
USE COLONCA.DBF INDEX CA.NDX
SEEK m_last
   IF .NOT. FOUND()      && IF THERE IS NO MATCH THEN EXITS THE PROGRAM
      m_initgo = .T.     && ALLOWS INITIATION SCREENS TO COME UP
      CLOSE DATABASES
      EXIT
   ENDIF

* This section lists all of the duplications in the database file

  DO WHILE LTRIM(TRIM(LASTNAME)) = m_last .AND. .NOT. EOF()
          IF TRIM(FIRSTNAME) = m_first .AND. DOB = m_dob
          @ 1,10 SAY ' YOUR PATIENT IS ALREADY  IN THE DATABASE'
          m_ednum = RECNO()
          @ 3,10 SAY TRIM(LASTNAME)+', '+TRIM(FIRSTNAME)+', ';
          +DTOC(DOB)+'.'
          CLOSE DATABASES
          WAIT
          EXIT
          ELSE
          @ 1,10 SAY ' THERE IS NO EXACT MATCH BUT HOW ABOUT..'
          LIST WHILE TRIM(LASTNAME) = m_last ;
          LASTNAME, FIRSTNAME, DOB
@ 22,5 SAY ' CHOOSE THE RECORD NUMBER OF THE FILE TO EDIT'
@ 23,5 SAY ' OR ZERO (0), TO EXIT.' GET m_ednum PICTURE '99999'
             READ
          CLEAR
             IF m_ednum < 1
                EXIT
             ENDIF
          GOTO m_ednum
          @ 10,10 SAY ' YOU ARE GOING TO EDIT THE FILES FOR '
          @ 11,10 SAY TRIM(LASTNAME) + ', ' + TRIM(FIRSTNAME) + ;
          '. ' + DTOC(DOB) + '.'
          m_last = LASTNAME
          m_first = FIRSTNAME
          m_dob = DOB
          CLOSE DATABASES
          ENDIF
         EXIT
        ENDDO    &&   THIS ENDS THE READ OUT OF THE PATIENTS DUPLICATES
  IF m_ednum < 1
     m_initgo = .T.
     EXIT
  ENDIF
CLOSE DATABASES
CLEAR

@ 13,10 SAY ' PRESS ANY KEY TO GO ON, X, TO EXIT' GET m_ans
READ
```

```
    IF UPPER(m_ans) = 'X'
       m_goback =.T.
    EXIT
    ENDIF
m_colptid = .F.
EXIT
ENDDO

RETURN
```

```
* PROGRAM...: COLINIT.PRG
* AUTHOR....: TONY MILES
* COPYRIGHT.: TONY MILES
* NOTE......: INITIATES THE SCREENS FOR THE FILES
* CALLED FROM OPEN.PRG
* The next section initiates a new set of screens for patients
* not already in the database

* Say a warning message to prevent initiation of unwanted screens

   @ 5,31 SAY 'WARNING'
   @ 4,29 TO 6,39 DOUBLE
   @ 13,10 SAY ' YOU ARE ABOUT TO INITIATE A NEW SET OF SCREENS'
   @ 14,10 SAY ' THE SCREENS WILL BE FOR '

* Say the name of the patient who's screens you are about to make

   @ 16,10 SAY m_last+', '+m_first+'. '+DTOC(m_dob)
   @ 15,8 TO 17,65 DOUBLE
   @ 18,10 SAY ' IT IS IMPOSSIBLE REMOVE THIS INFORMATION'
   @ 19,10 SAY ' IF YOU ARE NOT SURE GET OUT BY PRESSING X,'
   @ 20,10 SAY ' IF YOU ARE SURE YOU WANT TO GO ON PRESS Y,'
   m_ans = " "
   @ 22,40 GET m_ans PICTURE "!"
   READ
      DO WHILE .NOT. m_ans $ 'XY'
         @ 22,0
         m_ans = " "
         @ 22,10 SAY ' YOU MUST ANSWER Y OR X ' GET m_ans  ;
PICTURE "!"
         READ
      ENDDO
      IF m_ans = "X"
         CLEAR
         m_goback = .T.
         RETURN
      ENDIF

* this section initiates the actual files for the database


         USE COLONCA.DBF INDEX CA.NDX
         GO BOTTOM
            DO WHILE .NOT. EOF()
               SKIP
            ENDDO
         APPEND BLANK
         REPLACE LASTNAME WITH m_last
         REPLACE FIRSTNAME WITH m_first
         REPLACE DOB WITH m_dob
         REPLACE LINK WITH m_link
         m_ednum = RECNO()
         USE COLONCAP.DBF INDEX CAP.NDX
          GO BOTTOM
              DO WHILE .NOT. EOF()
                  SKIP
              ENDDO
          APPEND BLANK
          REPLACE LASTNAME WITH m_last
          REPLACE FIRSTNAME WITH m_first
          REPLACE DOB WITH m_dob
```

```
   REPLACE LINK WITH m_link
   USE COLONCAO.DBF INDEX CAO.NDX
   GO BOTTOM
       DO WHILE .NOT. EOF()
          SKIP
       ENDDO
   APPEND BLANK
   REPLACE LASTNAME WITH m_last
   REPLACE FIRSTNAME WITH m_first
   REPLACE DOB WITH m_dob
   REPLACE LINK WITH m_link
   USE COLONCAU.DBF INDEX CAU.NDX
   GO BOTTOM
       DO WHILE .NOT. EOF()
             SKIP
       ENDDO
   APPEND BLANK
   REPLACE LASTNAME WITH m_last
   REPLACE FIRSTNAME WITH m_first
   REPLACE DOB WITH m_dob
   REPLACE LINK WITH m_link
   USE COLONCAI.DBF INDEX CAI.NDX
    GO BOTTOM
        DO WHILE .NOT. EOF()
                   SKIP
        ENDDO
   APPEND BLANK
   REPLACE LASTNAME WITH m_last
   REPLACE FIRSTNAME WITH m_first
   REPLACE DOB WITH m_dob
   REPLACE LINK WITH m_link
   USE COLONCAR.DBF INDEX CAR.NDX
   GO BOTTOM
      DO WHILE .NOT. EOF()
            SKIP
      ENDDO
   APPEND BLANK
   REPLACE LASTNAME WITH m_last
   REPLACE FIRSTNAME WITH m_first
   REPLACE DOB WITH m_dob
   REPLACE LINK WITH m_link
   USE COLONCAB.DBF INDEX CAB.NDX
   GO BOTTOM
      DO WHILE .NOT. EOF()
         SKIP
      ENDDO
   APPEND BLANK
  REPLACE LASTNAME WITH m_last
  REPLACE FIRSTNAME WITH m_first
  REPLACE DOB WITH m_dob
  REPLACE LINK WITH m_link
USE COLONCAC.DBF INDEX CAC.NDX
GO BOTTOM
   DO WHILE .NOT. EOF()
      SKIP
   ENDDO
 APPEND BLANK
REPLACE LASTNAME WITH m_last
REPLACE FIRSTNAME WITH m_first
REPLACE DOB WITH m_dob
REPLACE LINK WITH m_link
CLEAR
```

```
        CLOSE DATABASES

RETURN
```

```
** THIS IS A PROGRAM TO DO CHISQ
** i WROTE iT
** 1994
m_A=0000
m_B=0000
m_C=0000
m_D=0000
m_1=00000000000
m_2=0
m_3=0
m_4=0
m_5=0
m_6=0
m_7=0
m_8=0
m_9=0
m_10=0
m_11=0
m_12=0


INPUT "ENTER A" TO m_A
INPUT "ENTER B" TO m_B
INPUT "ENTER C" TO m_C
INPUT "ENTER D" TO m_D

m_1=m_1+m_A
m_1=m_1+m_B
m_1=m_1+m_C
m_1=m_1+m_D

m_2= m_A*m_D
m_3= m_B*m_C
m_4= m_2-m_3
m_5= m_4*m_4
m_6= m_5*m_1
m_7= (m_A+m_B)
m_8= (m_C+m_D)
m_9= (m_B+m_D)
m_10=(m_A+m_C)
m_11= m_7*m_8*m_9*m_10
m_12= m_6/m_11
? m_12
```

```
. display structure
Structure for database: C:survival.dbf
Number of data records:     149
Date of last update    : 10/11/94
Field  Field Name  Type       Width    Dec
    1  LINK        Character     40
    2  DATERX      Date           8
    3  AGEDIG      Numeric        3
    4  WTLOSS      Logical        1
    5  CEA         Numeric        4
    6  SURGGRADE   Character      4
    7  CURE        Logical        1
    8  DATEOFDEAT  Date           8
    9  DEAD        Logical        1
   10  METFINAL    Logical        1
   11  IOEYN       Logical        1
   12  CODE        Character      3
** Total **                     76

.
Command Line     :<C:>:SURVIVAL                :Rec: EOF/149       :Ins

                        Enter a dBASE III PLUS command.
```

Record#	daterx	agedig	cea	surggrade	dateofdeat	metfinal	code	wtloss
1	10/10/90	43	30	CONS	/ /	.F.	C1	.T.
2	04/22/90	74	738	SR	05/02/90	.T.	C2	.T.
3	02/08/90	65	40	SR	/ /	.T.	B	.F.
4	10/22/90	57	30	CONS	/ /	.F.	C2	.F.
5	11/17/90	62	30	SR	/ /	.F.	C1	.F.
6	10/23/90	61	1040	CONS	01/31/93	.T.	C	.F.
7	04/24/90	76	339	CONS	05/03/90	.T.		.T.
8	06/04/90	63	78	CONS	05/09/91	.F.	B	.F.
9	12/24/90	65	0	SR	12/27/90	.F.	C	.F.
10	10/11/90	79	545	SR	02/18/94	.F.	B	.T.
11	05/10/90	62	97	CONS	/ /	.T.	A	.F.
12	09/26/90	69	102	CONS	/ /	.F.	B	.T.
13	08/21/90	77	30	CONS	/ /	.F.	B	.F.
14	07/31/90	76	93	CONS	10/29/93	.F.	B	.F.
15	11/12/90	80	66	CONS	/ /	.F.	B	.T.
16	09/28/90	88	101	CONS	/ /	.T.	B	.T.
17	01/01/91	78	30	CONS	04/04/92	.T.	C1	.F.
18	05/09/90	61	56	PROF	/ /	.F.	A	.T.
19	07/16/90	75	30	CONS	/ /	.F.	C1	.F.
20	10/24/90	50	39	CONS	/ /	.F.	B	.F.
21	10/29/90	70	115	CONS	/ /	.F.	C	.T.
22	11/05/90	78	55	SR	/ /	.F.	B	.F.
23	08/03/90	46	30	SR	/ /	.F.	C1	.F.
24	09/12/90	56	92	CONS	12/28/91	.T.	C1	.T.
25	03/29/90	82	30	CONS	04/25/90	.T.	B	.F.
26	05/18/90	75	49	CONS	/ /	.F.	B	.F.
27	11/27/90	61	30	SR	/ /	.F.	B	.F.
28	10/03/90	66	30	CONS	08/29/92	.F.	C	.F.
29	10/04/90	67	194	CONS	06/13/92	.F.	C1	.T.
30	11/27/90	80	30	CONS	/ /	.F.	B	.F.
31	11/29/90	61	787	CONS	10/28/92	.F.	C1	.F.
32	08/23/90	70	30	CONS	/ /	.F.	B	.T.
33	10/24/90	83	30	REG	/ /	.F.	B	.F.
34	03/22/90	76	131	CONS	01/20/92	.F.	C1	.F.
35	12/11/90	80	30	SR	/ /	.F.	C1	.F.
36	07/19/90	74	306	CONS	07/25/92	.F.	C1	.F.
37	08/02/90	55	30	CONS	/ /	.T.	C2	.T.
38	09/05/90	55	30	CONS	/ /	.F.		.F.
39	11/28/90	71	51	CONS	/ /	.F.	A	.F.
40	09/05/90	76	45	CONS	/ /	.F.		.F.
41	08/27/90	83	30	CONS	/ /	.F.		.F.
42	07/30/90	76	41	SR	/ /	.F.		.T.
43	08/20/90	81	0	REG	09/06/90	.F.		.F.
44	05/16/90	86	67	CONS	/ /	.F.	A	.F.
45	10/26/90	93	356	SR	10/17/92	.F.	C2	.F.
46	05/30/90	67	425	CONS	10/10/90	.F.		.T.
47	10/10/90	66	58	SR	/ /	.F.	B	.F.
48	11/28/90	79	30	CONS	/ /	.F.		.F.
49	05/16/90	76	30	CONS	06/20/90	.F.		.T.
50	07/16/90	84	30	CONS	/ /	.F.		.T.
51	07/04/90	66	1000	CONS	09/24/90	.T.		.T.
52	04/05/90	82	374	CONS	04/30/91	.T.	C2	.T.
53	08/08/90	75	1280	CONS	03/27/94	.F.	C2	.T.
54	10/17/85	60	84	CONS	/ /	.T.	B	.T.
55	05/15/90	66	913	REG	10/04/91	.F.	B	.F.
56	09/05/90	86	46	CONS	/ /	.F.	B	.F.
57	11/26/90	77	149	REG	12/30/90	.F.	B	.T.
58	08/22/90	53	4740	SR	/ /	.F.		.T.
59	03/15/90	69	340	SR	05/01/91	.F.	B	.T.
60	08/02/90	78	194	SR	11/21/91	.T.	A	.T.

61	12/19/90	78	32	SR	04/06/91	.F.	C1	.T.
62	12/04/90	63	117	SR	03/15/93	.F.	C1	.T.
63	12/19/90	80	119	CONS	/ /	.F.	C1	.F.
64	01/10/90	77	504	CONS	06/05/91	.F.	C1	.F.
65	11/16/90	59	919	SR	/ /	.F.	B	.T.
66	12/05/90	83	35	SR	02/24/93	.F.	C1	.F.
67	01/09/91	67	77	CONS	/ /	.F.		.T.
68	01/29/91	66	44	CONS	12/06/92	.F.	C1	.F.
69	02/19/91	83	44	CONS	/ /	.F.	A	.F.
70	01/29/91	72	159	SR	07/01/93	.F.	C1	.T.
71	02/13/91	69	86	CONS	/ /	.F.		.T.
72	02/14/91	78	36	CONS	/ /	.F.	C1	.F.
73	02/14/91	60	53	CONS	/ /	.F.	B	.F.
74	02/18/91	53	69	SR	/ /	.F.	B	.F.
75	01/14/91	81	2000	SR	06/01/91	.T.		.F.
76	01/28/91	69	105	SR	07/19/93	.F.	C1	.F.
77	10/22/90	74	30	CONS	/ /	.F.	B	.F.
78	01/14/91	62	500	CONS	/ /	.T.	C1	.T.
79	02/14/91	78	32	CONS	01/29/92	.F.	B	.F.
80	02/21/91	72	36	CONS	05/01/91	.F.	B	.T.
81	02/21/91	69	65	CONS	/ /	.F.	C1	.T.
82	04/09/90	76	30	CONS	/ /	.F.	B	.T.
83	02/04/91	55	167	REG	04/18/93	.T.	C1	.F.
84	02/25/91	83	73	CONS	/ /	.F.	A	.T.
85	07/09/90	70	500	CONS	01/21/91	.T.	C2	.T.
86	06/28/90	61	1600	CONS	10/17/92	.T.		.F.
87	03/12/91	81	93	CONS	08/19/91	.F.	C1	.F.
88	04/10/91	86	40	SR	/ /	.F.		.T.
89	04/16/91	67	30	CONS	08/13/91	.T.	C1	.F.
90	03/04/91	68	85	PROF	10/31/91	.F.	C1	.F.
91	02/27/91	76	30	SR	05/28/91	.F.	B	.T.
92	04/22/91	54	33	SR	10/25/91	.T.		.T.
93	05/22/91	51	60	SR	/ /	.F.	B	.F.
94	12/13/90	62	49	CONS	/ /	.F.	C1	.F.
95	04/18/91	77	34	CONS	/ /	.T.	C1	.F.
96	11/21/90	62	39	CONS	/ /	.F.	B	.F.
97	06/17/91	63	96	CONS	/ /	.F.	B	.T.
98	01/18/91	79	65	SR	07/06/91	.F.		.F.
99	05/02/91	71	30	CONS	/ /	.F.	B	.T.
100	06/27/91	74	68	SR	/ /	.F.	B	.T.
101	05/27/91	71	172	CONS	/ /	.F.	C1	.F.
102	05/04/91	62	30	SR	08/23/93	.T.	C1	.T.
103	06/27/91	86	213	SR	10/06/92	.F.	B	.T.
104	05/02/91	43	49	CONS	11/30/93	.T.	C1	.F.
105	10/21/91	59	30	SR	02/04/94	.F.	C2	.T.
106	10/01/91	78	91	CONS	/ /	.F.	B	.F.
107	10/10/91	68	645	CONS	07/09/92	.T.	C1	.T.
108	09/10/91	76	47	CONS	/ /	.F.	A	.T.
109	06/26/91	76	1200	CONS	11/01/93	.T.	C2	.F.
110	10/21/91	82	74	CONS	/ /	.F.		.F.
111	05/02/91	71	205	CONS	02/10/93	.F.	C2	.F.
112	11/04/91	77	62	SR	01/28/94	.T.	B	.F.
113	03/07/91	71	55	CONS	/ /	.F.		.F.
114	09/04/91	75	30	SR	10/24/92	.F.	C1	.T.
115	06/27/90	71	70	REG	/ /	.F.		.T.
116	02/12/91	68	389	SR	/ /	.F.	B	.T.
117	08/13/91	76	248	SR	01/27/92	.T.	C1	.T.
118	07/18/91	64	30	CONS	/ /	.F.		.F.
119	09/09/91	72	45	SR	/ /	.F.	B	.T.
120	08/05/91	85	88	SR	/ /	.F.	B	.F.
121	05/01/91	68	48	SR	/ /	.F.	CI	.T.
122	10/11/91	73	35	CONS	/ /	.F.	A	.F.

123	03/14/91	52	249	CONS	05/12/93	.T.			.F.
124	04/17/91	70	2000	CONS	12/22/91	.T.		D	.T.
125	02/12/91	74	34	CONS	/ /	.F.		B	.F.
126	10/22/90	66	0	CONS	/ /	.T.			.F.
127	02/18/91	65	30	CONS	/ /	.F.		C1	.F.
128	04/22/91	57	36	SR	10/09/91	.T.		C	.F.
129	10/29/91	84	90	CONS	07/22/92	.T.		B	.T.
130	10/10/91	78	31	SR	/ /	.T.		A	.F.
131	10/30/91	74	0	SR	/ /	.F.			.F.
132	09/18/91	46	30	CONS	/ /	.F.		C2	.T.
133	12/04/91	84	55	CONS	/ /	.F.		C	.F.
134	12/04/91	44	54	SR	/ /	.F.		B	.T.
135	12/09/91	58	30	REG	/ /	.F.		C1	.F.
136	12/12/91	58	0	REG	12/28/93	.T.		B	.T.
137	12/11/91	84	50	CONS	/ /	.F.		C1	.F.
138	11/06/91	58	38	CONS	05/14/92	.T.		C2	.F.
139	01/09/92	65	43	CONS	/ /	.F.		B	.F.
140	01/10/92	63	1090	REG	02/25/92	.T.		C	.F.
141	02/05/92	78	0	REG	02/12/92	.T.			.T.
142	02/06/92	69	55	CONS	/ /	.F.		B	.T.
143	01/29/92	37	0	CONS	/ /	.T.		C	.T.
144	02/25/92	76	1600	CONS	/ /	.F.		B	.T.
145	11/11/91	73	0	CONS	/ /	.T.		B	.F.
146	02/20/92	68	30	CONS	/ /	.F.		C	.T.
147	03/13/92	59	37	SR	/ /	.T.		B	.T.
148	03/05/92	43	74	REG	/ /	.T.		B	.F.
149	11/18/91	72	30	SR	01/09/93	.F.			.T.

Structure for database: C:colonca.dbf
Number of data records: 155
Date of last update : 07/09/94

Field	Field Name	Type	Width	Dec
1	CIS	Character	1	
2	LINK	Character	40	
3	OTHERFIND	Memo	10	
4	MEMFIELD	Logical	1	
5	MALAISE	Logical	1	
6	CONSTIPAT	Logical	1	
7	OTHER	Memo	10	
8	TELNO	Character	12	
9	LASTNAME	Character	25	
10	FIRSTNAME	Character	25	
11	ADDRESS	Character	60	
12	PCODE	Character	10	
13	DOB	Date	8	
14	SEX	Character	2	
15	CONS	Character	25	
16	WEIGHT	Numeric	3	
17	HEIGHT	Numeric	4	
18	AGEDIG	Numeric	3	
19	ETHNIC	Character	3	
20	GPNAME	Character	25	
21	GPADDRESS	Character	60	
22	GPCODE	Character	10	
23	OCC	Character	20	
24	DATESS	Date	8	
25	DATEGP	Date	8	
26	DATEHC	Date	8	
27	DATED	Date	8	
28	DATERX	Date	8	
29	GICA	Logical	1	
30	GICAD	Date	8	
31	GICAF	Character	10	
32	GICAFD	Numeric	3	
33	FAP	Logical	1	
34	FAPD	Date	8	
35	FAPF	Character	10	
36	FAPFD	Numeric	3	
37	LBA	Logical	1	
38	LBAD	Date	8	
39	LBAF	Character	10	
40	LBAFD	Numeric	3	
41	UC	Logical	1	
42	UCD	Date	8	
43	UCF	Character	10	
44	UCFD	Numeric	3	
45	CD	Logical	1	
46	CDD	Date	8	
47	CDF	Character	10	
48	CDFD	Numeric	3	
49	OC	Logical	1	
50	OCD	Date	8	
51	OCSITE	Character	20	
52	OCF	Character	10	
53	OCFD	Numeric	3	
54	OCFSITE	Character	20	
55	MI	Logical	1	
56	MID	Date	8	
57	MIF	Character	10	

58	MIFD	Date	8
59	CHOLE	Logical	1
60	CHOLEDATE	Date	8
61	ULCERSURG	Logical	1
62	ULCERSURGD	Date	8
63	GUTSURG	Logical	1
64	GUTSURGD	Date	8
65	DURG1	Character	40
66	DRUG2	Character	40
67	DRUG3	Character	40
68	DRUG4	Character	40
69	DRUG5	Character	40
70	DRUG6	Character	40
71	DURG7	Character	40
72	DRUG8	Character	40
73	PRES	Character	3
74	SYMP	Character	1
75	ABDOPAIN	Logical	1
76	CHOFHABIT	Logical	1
77	DIARRHOEA	Logical	1
78	PRBLEED	Logical	1
79	MELENA	Logical	1
80	SYMOFANAE	Logical	1
81	MUCUS	Logical	1
82	TENESMUS	Logical	1
83	ANOREXIA	Logical	1
84	WTLOSS	Logical	1
85	DISTENSION	Logical	1
86	MASS	Logical	1
87	BLEED	Logical	1
88	SIGNS	Logical	1
89	PALLOR	Logical	1
90	JAUNDICE	Logical	1
91	EVWTLOSS	Logical	1
92	GASDIST	Logical	1
93	ASCTIES	Logical	1
94	EVMASS	Character	1
95	EVMASSSIZE	Numeric	3
96	LIVERPALP	Logical	1
97	PRMASS	Character	1
98	PRMCIRC	Numeric	3
99	QUAD	Character	1
100	EXTMASS	Character	1
101	BLOODPR	Logical	1
102	FOB	Logical	1
103	SIGOUT	Numeric	3
** Total **			985

Structure for database: C:coloncab.dbf
Number of data records: 155
Date of last update : 03/20/94

Field	Field Name	Type	Width	Dec
1	CIS	Character	1	
2	LINK	Character	40	
3	LASTNAME	Character	25	
4	FIRSTNAME	Character	25	
5	DOB	Date	8	
6	CXR	Character	1	
7	BAENEMA	Character	2	
8	SIGRF	Character	1	
9	SIGPATH	Character	2	
10	COLONOSC	Character	2	
11	BX	Character	2	
12	BXPATH	Character	2	
13	FNACL	Character	2	
14	FNACT	Character	2	
15	WBB	Numeric	5	2
16	RBC	Numeric	5	2
17	HB	Numeric	5	2
18	HCT	Numeric	5	2
19	MCV	Numeric	6	2
20	MCH	Numeric	4	1
21	MCHC	Numeric	4	1
22	PLATS	Numeric	4	
23	GRAN	Numeric	5	2
24	LYMPH	Numeric	5	2
25	MONO	Numeric	5	2
26	EOSIN	Numeric	5	2
27	BASO	Numeric	5	2
28	ESR	Numeric	3	
29	NA	Numeric	4	
30	K	Numeric	5	2
31	CL	Numeric	4	
32	CO2	Numeric	3	
33	U	Numeric	5	2
34	LD	Numeric	4	
35	ALT	Numeric	4	
36	ALKPHOS	Numeric	4	
37	BIL	Numeric	4	
38	GGT	Numeric	4	
39	TOTPROT	Numeric	3	
40	ALB	Numeric	3	
41	CEA	Numeric	4	
42	CA_19_9	Numeric	3	
43	TNF	Numeric	4	
44	FERITIN	Numeric	4	
** Total **			244	

Structure for database: C:coloncao.dbf
Number of data records: 155
Date of last update : 08/23/94

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1	CIS	Character	1	
2	LINK	Character	40	
3	OP3	Character	25	
4	OP2	Character	25	
5	OP1	Character	25	
6	PRIMARY	Character	3	
7	WOUNDINF	Character	2	
8	CONSTUCT	Character	2	
9	DOUGHNUT	Logical	1	
10	GUN	Character	3	
11	OTHERINV	Memo	10	
12	LOCALINV3	Character	2	
13	LOCALINV2	Character	2	
14	ASSTGRADE	Character	4	
15	SURGGRADE	Character	4	
16	LASTNAME	Character	25	
17	FIRSTNAME	Character	25	
18	DOB	Date	8	
19	CA1SITE	Character	2	
20	CA2SITE	Character	2	
21	OPCODE1	Character	7	
22	OPCODE2	Character	7	
23	OPCODE3	Character	7	
24	COLOSTOMY	Logical	1	
25	EMERG	Character	2	
26	SURG	Character	25	
27	ASSIST	Character	25	
28	METS	Character	1	
29	MET1S	Character	3	
30	MET2S	Character	3	
31	MET3S	Character	3	
32	MET4S	Character	3	
33	MET5S	Character	3	
34	MET6S	Character	3	
35	MET7S	Character	3	
36	MET8S	Character	3	
37	MET9S	Character	3	
38	MET10S	Character	3	
39	MET1D	Numeric	3	
40	MET2D	Numeric	3	
41	MET3D	Numeric	3	
42	MET4D	Numeric	3	
43	MET5D	Numeric	3	
44	MET6D	Numeric	3	
45	MET7D	Numeric	3	
46	MET8D	Numeric	3	
47	MET9D	Numeric	3	
48	MET10D	Numeric	3	
49	MET1B	Character	1	
50	MET2B	Character	1	
51	MET3B	Character	1	
52	MET4B	Character	1	
53	MET5B	Character	1	
54	MET6B	Character	1	
55	MET7B	Character	1	
56	MET8B	Character	1	
57	MET9B	Character	1	

58	MET10B	Character	1
59	MET1P	Character	1
60	MET2P	Character	1
61	MET3P	Character	1
62	MET4P	Character	1
63	MET5P	Character	1
64	MET6P	Character	1
65	MET7P	Character	1
66	MET8P	Character	1
67	MET9P	Character	1
68	MET10P	Character	1
69	LOCALINV	Character	2
70	MOBILITY	Character	1
71	CURE	Logical	1
72	BXOTHER	Character	1
73	AMASTAMO	Character	1
74	L1	Character	1
75	L2	Character	1
76	STAPLED	Character	10
77	DBCLOSE	Character	1
78	SIGINF	Logical	1
79	COLOSHIELD	Logical	1
80	BOWELLEV	Logical	1
81	TETRACYCLI	Logical	1
82	DRAINS	Character	2
83	BLOODTX	Character	2
84	ANASLEAK	Character	2
85	CHESTINF	Character	2
86	ABDOCOLLEC	Character	2
87	WOUNDHAEM	Character	2
88	WOUNDBURST	Character	2
89	INTBLEED	Character	2
90	STOMA	Character	2
91	HOSPDAYS	Numeric	3
92	ABXDAYS	Numeric	3
93	DEATH	Logical	1
94	DEATHDAYS	Numeric	3
95	CAUSE	Character	25
96	CERT1	Character	25
97	CERT2	Character	25
98	CERT3	Character	25
99	ICD_CODE	Character	10
** Total **			528

Structure for database: C:coloncai.dbf
Number of data records: 155
Date of last update : 10/11/94

Field	Field Name	Type	Width	Dec
1	SCANNUM	Character	1	
2	CIS	Character	1	
3	LINK	Character	40	
4	HAEMANUM	Numeric	2	
5	CYSTNUM	Numeric	2	
6	EXCLUDED	Character	2	
7	LASTNAME	Character	25	
8	FIRSTNAME	Character	25	
9	DOB	Date	8	
10	CTRUNNUM	Numeric	12	
11	METS	Character	1	
12	MET1S	Character	3	
13	MET2S	Character	3	
14	MET3S	Character	3	
15	MET4S	Character	3	
16	MET5S	Character	3	
17	MET6S	Character	3	
18	MRT7S	Character	3	
19	MET8S	Character	3	
20	MET9S	Character	3	
21	MET10S	Character	3	
22	MET1D	Numeric	4	
23	MTS2D	Numeric	4	
24	MET3D	Numeric	4	
25	MET4D	Numeric	4	
26	MET5D	Numeric	4	
27	MET6D	Numeric	4	
28	MET7D	Numeric	4	
29	MET8D	Numeric	4	
30	MET9D	Numeric	4	
31	MET10D	Numeric	4	
32	MET1V	Numeric	4	
33	MET2V	Numeric	4	
34	MET3V	Numeric	4	
35	MET4V	Numeric	4	
36	MET5V	Numeric	4	
37	MET6V	Numeric	4	
38	MET7V	Numeric	4	
39	MET8V	Numeric	4	
40	MET9V	Numeric	4	
41	MET10V	Numeric	4	
42	TOTVOL	Numeric	4	
43	TOTLIVVOL	Numeric	4	
44	PERCENTCA	Numeric	3	
45	RTEMP	Numeric	4	1
46	RPULSE	Numeric	3	
47	RBP	Character	8	
48	HTEMP	Numeric	4	1
49	HPULSE	Numeric	3	
50	HBP	Character	8	
51	LOWTEMP	Numeric	4	1
52	LOWPULSE	Numeric	3	
53	LOWBP	Character	8	
54	RIGORS	Logical	1	
55	HEADACHE	Logical	1	
56	METALTASTE	Logical	1	
57	ANOEDEMA	Logical	1	

58	OTHERREACT	Memo	10
59	IOEYN	Character	1
** Total **			301

Appendix 4

Data collection sheets

COLO-RECTAL CANCER STUDY

NAME_____ DOB_____

HOSPITAL NUMBER_____ SEX M\F _____

ADDRESS_____ CONSULTANT_____

_____ _____

_____ WEIGHT_____kgs

POST CODE_____ HEIGHT_____cms

GP NAME_____ AGE AT DIAGNOSIS_____yr

ADDRESS_____ ETHNIC GROUP CAUCASIAN

_____ ASIAN

CHANGE_____ AFRO CARIB

_____ OTHER

OCCUPATION_____

DATE OF .....START OF SYMPTOMS __/__/__

SEEING G.P. __/__/__

HOSPITAL CONSULT' __/__/__

DIAGNOSIS __/__/__

START OF TREATMENT /OPERATION __/__/__

PREVIOUS MEDICAL HISTORY

		YEAR
GI CANCER	Y__ N__ NK__	_____
FAP	Y__ N__ NK__	_____
LARGE BOWEL ADENOMA	Y__ N__ NK__	_____
ULCERATIVE COLITIS	Y__ N__ NK__	_____
CROHN'S DISEASE	Y__ N__ NK__	_____
OTHER CANCER	Y__ N__ NK__	_____
MI	Y__ N__ NK__	_____
OTHER_____		
CHOLECYSTECTOMY	Y__ N__ NK__	_____
PEPTIC ULCER SURGERY	Y__ N__ NK__	_____
BOWEL SURGERY	Y__ N__ NK__	_____

FAMILY HISTORY

		YEAR
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
	Y__ N__ NK__	_____
_____		
YEAR_____		
YEAR_____		
YEAR_____		

DRUGS _____

_____

_____

_____

_____

_____

_____

_____

PRESENTATION

ELECTIVE_____ EMERGENCY_____ OBSTRUCTION_____
PERFORATION_____
HAEMORRHAGE_____

SYMPTOMS		PHYSICAL FINDINGS	
NONE	____	NO SIGNS	____
ABDO PAIN	____	PALLOR	____
CHANGE OF HABIT	____	JAUNDICE	____
DIARRHOEA	____	EVIDENT WT LOSS	____
CONSTIPATION	____	GASEOUS DISTENSION	____
PR BLEEDING	____	ASCITES	____
MELAENA	____	MASS MOBILE/TETHERED/FIXED	
SYMPTOMS OF ANAEMIA	____	SIZE_____cms	
MUCUS	____	PALPABLE LIVER	____
TENESMUS	____	PR MASS (DIGITAL EXAM)	
MALAISE	____	MOBILE/TETHERED/FIXED	
ANOREXIA	____	CIRCUM % <25,<50,<75,<=100.	
WT LOSS	____	QUADRANT ANT,RIGHT,POST,LEFT	
DISTENSION	____	EXTRINSIC PR MASS	
MASS	____	MOBILE/TETHERED/FIXED	
MAJOR BLEED	____	BLOOD	____
		FOB	____
		OTHER SIGNS	

DISTANCE FROM ANUS ___CM__ BY RIGID SIGMOIDOSCOPY

OTHER FINDINGS _____

_____

_____

_____

PHYSICAL INVESTIGATIONS (GENERAL)

CHEST X RAY	NORMAL / SUSP / POS
BA ENEMA	NORMAL / SUSP / POS / POLYPS / SYNC CA / FAIL
SIGMOIDOSCOPY R/F	NORMAL / POS / POLYPS / SYNC CA / FAIL / N.D.
COLONOSCOPY	NORMAL / POS / POLYPS / SYNC CA / FAIL / N.D.

BIOPSY

GAINED BY	R'SIG / F'SIG / COLONOS' / FNAC
PATH	NORMAL / SUSP / CANCER / POLYP
FNAC LIVER	NEG / SUSP / POS / OTHER / ND
FNAC MASS	NEG / SUSP / POS / OTHER / ND

PHYSICAL PARAMETERS

WEIGHT	ACTUAL____kg	IDEAL____kg
HEIGHT	ACTUAL____cm	IDEAL____cm
MAMC	ACTUAL____	IDEAL____
TST	ACTUAL____cm	IDEAL____cm
DYNAMOMETRY	ACTUAL____	IDEAL____

HAEMATOLOGY

WCC	____	RETICS	___	NA	____
RBC	____			K	____
HB	____			Cl	____
HCT	____			Co2	____
MCV	____			U	____
MCH	____			LD	____
MCHC	____			AST	____
PLATS	____			ALK PHOS	____
GRAN	____			BIL	____
LYMPH	____			GGT	____
MONO	____			TOT PROT	____
EOSIN	____			ALB	____
BASO	____			CEA	____
ESR	____			CA15-S	____

BIOCHEMISTRY

TNF	____
FERRITIN	____

INTRAOPERATIVE ULTRASOUND

ACCESS ADEQUATE____ INADEQUATE____

SCAN COMPLETE____ INCOMPLETE____

SCANNER ALOKA____ OTHER_____

SURGEON _____ GRADE_____

ANATOMICAL LANDMARKS CLEAR? CONFIDENCE HIGH____ LOW____

FINDINGS

CYSTS____ HAEMANGIOMA____

DESCRIPTION OF METASTASES RANKED BY SIZE

NUMBER	SEGMENT	DIAMETER	BIOPSY	PATH
1.	_____	_____	_____	____
2.	_____	_____	_____	____
3.	_____	_____	_____	____
4.	_____	_____	_____	____
5.	_____	_____	_____	____
6.	_____	_____	_____	____
7.	_____	_____	_____	____
8.	_____	_____	_____	____
9.	_____	_____	_____	____
10.	_____	_____	_____	____

SITE IS BY SEGMENT NUMBER

IF METASTASES >10 THEN SITE AND SIZE LARGEST SINGLE METASTASIS OR CONTIGUOUS GROUP.

OTHER NOTES

_____

_____

_____

_____

_____

_____

OPERATION
SITE

1st TUMOUR SITE CEACUM / ASC COLON / HEP FLEX / TRANS
SPL FLEX / DESC / SIGMOID
ABOVE / STRADDLING / BELOW REFLECTION

2nd TUMOUR SITE CEACUM / ASC COLON / HEP FLEX / TRANS
SPL FLEX / DESC / SIGMOID
ABOVE / STRADDLING / BELOW REFLECTION

OPERATION _____ CODE___/__/_____

_____ CODE___/__/_____

_____ CODE___/__/_____

PROTECTIVE COLOSTOMY / CEACOSTOMY

EMERGENCY (<24hrs) DELAYED EM (>24 hrs) ELECTIVE

SURGEON_____ GRADE_____

ASSISTANT_____ GRADE_____

METASTATIC SPREAD LIVER / LOCAL NODES / PARA AORTIC
PERITONEAL / OTHER

LIVER ASSESSMENT

NUMBER	SIZE(cm)	SITE	BIOPSY	PATH
1.	_____	_____	_____	_____
2.	_____	_____	_____	_____
3.	_____	_____	_____	_____
4.	_____	_____	_____	_____
5.	_____	_____	_____	_____
6.	_____	_____	_____	_____
7.	_____	_____	_____	_____
8.	_____	_____	_____	_____
9.	_____	_____	_____	_____
10.	_____	_____	_____	_____

LOCAL INVASION ABDO MUSCLE / PELVIC WALL MUSCLE / BLADDER
URETER / OTHER BOWEL / OVARY / UTERUS
UTERINE TUBE / LOCAL ABSCESS / PERFORATION
OTHER_____

MOBILITY OF TUMOUR MOBILE / TETHERED / FIXED

CURATIVE OPERATION YES / NO

BIOPSY NODES / SEEDLINGS / TUMOUR BED

OPERATIVE TECHNIQUE

ANASTOMOSIS NONE / STAPLED / SUTURED(ONE OR TWO LAYER)

LAYER ONE ABSORBABLE / NONABSORBABLE

LAYER TWO ABSORBABLE / NONABSORBABLE

STAPLED EEA / PROXIMATE(SIZE____cm) / GIA / PLC
DOUGHNUT OK YES/NO
END/END END/SIDE SIDE/END SIDE/SIDE

DISTAL BOWEL CLOSURE PURSE STRING / STAPLED

SIGMOIDOSCOPIC INFLATION CHECK YES / NO

COLOSHIELD YES / NO

ON TABLE BOWEL LAVAGE YES / NO

TETRACYCLINE LAVAGE YES / NO

DRAINS NONE / NONE SUCTION / SUCTION / SUCTION IRRIGATION

BLOOD TRANSFUSION NONE / PRE OP / PER OP / POST OP

POST OPERATION COMPLICATIONS

ANASTAMOTIC LEAK NONE / SUSP / PROVEN / RE OPERATION

CHEST INFECTION NONE / SUSP / PROVEN / TREATED

INTRA ABDOMINAL COLLECTION NONE / SUSP / PROVEN / DRAINED

WOUND HAEMATOMA NONE / OBSERVED / TREATED

WOUND INFECTION NONE / OBSERVED / ABX / DRAINED

WOUND DEHISCENCE NONE / SUPERFICIAL / DEEP (RE OP)

INTRAPERITONEAL BLEED NONE / MINOR / MAJOR / RE OP

STOMA RETRACTION / NECROSIS / REVISION

DAYS IN HOSPITAL _____DAYS

DAYS OF ANTIBIOTICS _____DAYS

DEATH YES / NO

CAUSE INFECTION / MI / CVA / PE / HAEMORRHAGE/OTHER

CERTIFIED CAUSE OF DEATH_____

1_____

2_____

3_____

I.C.D. CODE_____

PATHOLOGY

PATHOLOGIST_____ PATH #_____
FIXED / FRESH

LENGTH OF SPECIMEN_____cm LENGTH OF TUMOUR_____cm
CIRCUMFERENCE _____cm WIDTH OF TUMOUR_____cm
PROXIMAL CLEARANCE_____cm DISTAL CLEARANCE_____cm

APPEARANCE ULCERATING / PROTUBERANT / DIFFUSELY INFILTRATING

RELATION TO PERITONEAL REFLECTION ABOVE / STRADDLING / BELOW

LOCAL SPREAD

DYSPLASIA ONLY / SUBMUCOSA / MUSC PROPRIA / BEYOND MUSC PROP
THROUGH PERITONEUM / INTO OTHER ORGANS

DEPTH BEYOND MUSC PROP____mm BX OF TUMOUR BED POS / NEG / N.A.

MINIMUM CUMFERENTIAL MARGIN____mm

CONFIRMED HISTOLOGICALLY YES / NO LOCAL EXCISION YES / NO / ?

LYMPHATIC SPREAD

NODES EXAMINED #____ NODES POSITIVE #____

APICAL NODE POS / NEG / N.A.

INVASION OF LYMPHATIC SPACES YES / NO

INVASION OF PERINURAL SPACES YES / NO

EXTRAMURAL DEPOSITS NOT IN NODES YES / NO

INVASION OF EXTRAMURAL VEINS YES / NO

LIVER METS CONFIRMED YES / NO

PERITONEAL METS CONFIRMED YES / NO

PARA AORTIC NODES CONFIRMED YES / NO

PATH OF TUMOUR

ADENO CA / MUCINIOUS CA / SIGNET RING CA / OTHER_____

DIFFERENTIATION BY WORST AREA POOR / OTHER

DIFFRERNTIATION BY PREDOMINANT AREA POOR / OTHER

INVASIVE MARGIN EXPANDING / INFILTRATING

LYMPHOCYTES AT MARGIN CONSPICUOUS YES / NO

ADENOMAS YES / NO #____ SYNCHRONOUS CA YES / NO

ULCERATIVE COLITIS YES / NO F.A.P. YES / NO

CURATIVE / NONCURATIVE LOCAL SPREAD / NONCURATIVE DISTANT SPREAD
CODE A / B / C1 / C2

RADIOLOGY REPORT

RECTAL TUMOURS

HEIGHT OF LOWER BORDER FROM SPHINCTER _____cm
CIRCUMFERENTIAL INVOLVEMENT ANT / RIGHT / POST / LEFT QUADRANTS
LENGTH _____cm
RADIAL EXTENT OF TUMOUR
CONFINED TO BOWEL WALL _____
THROUGH WALL INTO PERI-RECTAL SPACE _____
THROUGH PERI-RECTAL FASCIA _____

COLONIC TUMOURS

SITE CEACUM / ASCENDING / TRANSVERSE / DESCENDING / SIGMOID
RADIAL EXTENT OF TUMOUR
CONFINED TO BOWEL WALL _____
THROUGH BOWEL WALL _____

DISTAL SPREAD
SACRUM / COCCYX / BLADDER / PROSTATE / SEMINAL VESICALS / UTERUS
PELVIC SIDE WALL / MUSCLE / URETERIC OBSTRUCTION / PERITONEAL SEEDLINGS / ASCITES

LYMPH NODE INVOLVEMENT

SIZE mm	<5	5-10	10-15	>15
WITHIN PERI-RECTAL FAT	—	—	—	—
OUTSIDE PERI-RECTAL FAT	—	—	—	—
INTERNAL ILIAC CHAIN	—	—	—	—
EXTERNAL ILIAC CHAIN	—	—	—	—
PARA-AORTIC RETRO-CURAL	—	—	—	—
MESENTERIC	—	—	—	—

LIVER INVOLVEMENT
C.T. UNENHANCED AND WITH WATER SOLUBLE CONTRAST
METASTATIC DEPOSITS YES / NO

NUMBER	SEGMENT INVOLVED		DIAMETER mm	
	NO CONTRAST	WS CONTRAST	NO CONTRAST	WS CONTRAST
1.	_____	_____	_____	_____
2.	_____	_____	_____	_____
3.	_____	_____	_____	_____
4.	_____	_____	_____	_____
5.	_____	_____	_____	_____
6.	_____	_____	_____	_____
7.	_____	_____	_____	_____
8.	_____	_____	_____	_____
9.	_____	_____	_____	_____
10	_____	_____	_____	_____

I.O.E. SCANS

METASTATIC DEPOSITS YES / NO

NUMBER	SEGMENT	MAX DIAMETER	VOLUME
1.	_____	_____	_____
2.	_____	_____	_____
3.	_____	_____	_____
4.	_____	_____	_____
5.	_____	_____	_____
6.	_____	_____	_____
7.	_____	_____	_____
8.	_____	_____	_____
9.	_____	_____	_____
10.	_____	_____	_____

IF MORE THAN 10 METS SPECIFY SITE (BY SEGMENT) OF LARGEST DEFINABLE MASS OR GROUP OF METS.

TOTAL VOLUME OF METASTATIC DEPOSITS _____ cm^3

TOTAL VOLUME OF NORMAL LIVER _____ cm^3

% LIVER REPLACED BY TUMOUR _____ %

REACTIONS TO SCAN

RESTING TEMP_____ PULSE_____ BP_____

HIGHEST TEMP_____ PULSE_____ BP_____

LOWEST TEMP_____ PULSE_____ BP_____

RIGORS YES / NO

HEADACHE YES / NO

METALLIC TASTE YES / NO

ANGIONEUROTIC OEDEMA YES / NO

OTHER REACTIONS_____

_____

_____

OTHER RADIOLOGY.

THORAX

CHEST XRAY NORMAL YES / NO

METASTASES YES / NO

NUMBER _____

MAX DIAMETER OF LARGEST MET _____cm

MEDIASTINUM NORMAL YES / NO

C.T.

MEDIASTINAL NODES YES / NO

SIZE OF LARGEST NODE IN mm <5 / 5-10 / 10-15 / >15

PULMONARY METASTASES YES / NO

NUMBER _____

MAX DIAMETER OF LARGEST DEPOSIT _____cm

OTHER_____

_____

_____

ULTRASOUND

RECTAL ULTRASOUND

NEGATIVE / MUCOSAL / MUSCLE / FULL THICKNESS / BEYOND

QUADRANT ANT / RIGHT / POST / LEFT

ABDOMINAL ULTRASOUND

INVOLVEMENT OF OTHER ABDOMINAL STRUCTURES YES / NO

IF YES BLADDER / PROSTATE / SEMINAL VESICLES / VAGINA / UTERUS / PELVIC SIDE WALLS / MUSCLE / URETERIC OBSTRUCTION / PERITONEAL SEEDLINGS / ASCITES

LYMPH NODES

	SIZE 5-10	10-15	>15
INTERNAL ILIAC CHAIN	____	____	____
EXTERNAL ILIAC CHAIN	____	____	____
PARA AORTIC CHAIN	____	____	____
MESENTERIC	____	____	____

LIVER

ULTRASOUND

METASTATIC DEPOSITS YES / NO

NUMBER	SEGMENT	MAX DIAMETER
1.	_____	_____
2.	_____	_____
3.	_____	_____
4.	_____	_____
5.	_____	_____
6.	_____	_____
7.	_____	_____
8.	_____	_____
9.	_____	_____
10.	_____	_____
IF MORE THAN TEN SPECIFY		_____

RADIO ISOTOPE

BONE SCAN YES / NO

NORMAL / METASTASES

OTHER SPECIFY _____

_____

_____

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